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An Audience with Pharmaceutical Regulators, Academia and Industry 2019: the Role of Quality Risk Management (QRM) and Knowledge Management (KM) in Medicinal Product Realisation for Patients in the 21st. Century

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The role of Quality Risk Management (QRM) and Knowledge Management (KM) in Medicinal Product Realisation for Patients in the 21st century

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OLLSCOIL TEICNEOLAÍOCHTA BHAILE ÁTHA CLIATH
TU DUBLIN
TECHNOLOGICAL UNIVERSITY DUBLIN

An Audience with Pharmaceutical Regulators, Academia and Industry

The role of Quality Risk Management (QRM) and Knowledge Management (KM) in Medicinal Product Realisation for Patients in the 21st century

A monograph

based on a seminar organised by The School of Chemistry & Pharmaceutical Science, Technological University Dublin, with the Health Products Regulatory Authority, and with Regulatory Science Ireland 4th April 2019

EDITORS: Anne Greene, Kevin O'Donnell, Anne Murphy and Elaine Harris

HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

RSI
REGULATORY SCIENCE IRELAND
WORKING TOGETHER FOR BETTER PATIENT OUTCOMES

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Foreword

In December 2018, on the ten-year anniversary of ICH Q10 'Pharmaceutical Quality System', the Dublin Institute of Technology (DIT) and the Health Products Regulatory Authority (HPRA) jointly published a monograph based on the presentations delivered at their joint seminar 'An Audience with International Regulators' held on 3rd October 2018 in the DIT. Since then, on 1 January 2019, DIT together with ITB and ITT, joined together to form Irelands first Technological University, Technological University Dublin (TU Dublin). On 4th April 2019, TU Dublin, together with HPRA and RSI held a follow-up seminar in St Laurence's Hall, TU Dublin, Grangegorman, and this monograph is based on the presentations and Q&A session at that seminar.

ICH Q10 describes a model for an effective quality management system for the pharmaceutical industry which advocates the use of Knowledge Management (KM) and Quality Risk Management (QRM) as enablers to achieve its 3 key objectives of Achieving Product Realisation, Establishing and Maintaining a State of Control, and Facilitating Continual Improvement. It proposes that QRM and KM would provide the means for science-based and risk-based decisions related to product quality. In the last 10 years it has been our privilege to work with regulatory and industry thought-leaders within the fields of QRM and KM. While many publications on both topics have been produced in the decade, they are usually treated as separate enablers. Our vision for this series of seminars, research work and resulting monographs is to further explore how QRM and KM work together to enhance our decision-making with respect to pharmaceutical product quality.

This monograph begins with *introductory matters* from Prof. Brian O'Neill, TU Dublin who introduced the vision of an academic press, and the important role it plays in desminatiating knowledge to the wider society. This is then followed by John Lynch, (HPRA) who highlighted the role of QRM in CGMP, and welcomes the inclusion of KM in the monograph. Finally in the opening section, Prof. Frank Hallinan gave an overview of RSI, and its vision for an Ireland response to Regulatory Science challenges.

The monograph then progresses to *regulatory matters* with a thought-provoking article by Dr Kevin O'Donnell from HPRA on demonstrating the effectiveness of the PQS from a QRM perspective.

The focus then shifts to *industry matters* as Hal Baseman presents an innovative approach to aseptic process intervention using risk assessment. Then Martine Nolan takes an overview look at the challenges faced manufacturing combination products in a traditional secondary packaging facility.

In a section titled *technology innovation matters* Dr Barry Heavey begins by introducing Pharma 4.0, demystify the techno-jargon and focus on the 'why'. This is followed by Luke Kiernan exploring the role of smart manufacturing in realising products for patients in the 21st century.

This leads us to the *PRST researchers' contributions*, starting with Knowledge Management, where Marty Lipa and Dr Paige Kane present their vision of advancing the dialogue to improve patient outcomes through

improved knowledge transfer. Ghada Haddad then turns to QRM, and presents a role-based competency module for individuals involved in QRM. This section finishes with a paper by the Eammon McGowan who presents an interesting overview of the roles QRM and KM play in innovation.

The monograph concludes with a summary of the interesting Q&A session which was facilitated by Bill Paulson and Dr Nuala Calnan with all the presenters taking part in the Panel Discussion.

On behalf of all the authors and the editorial team, I hope you enjoy this monograph and that it will encourage further dialogue and exploration of the interaction between both QRM and KM, the twin enablers identified in ICH Q10.

Anne Greene
June 2019

Contributor and Editor Profiles

Brian O'Neill • PhD, Director of Research and Enterprise, Dean of the Graduate Research School, TU Dublin

Professor Brian O'Neill is Director of Research, Enterprise & Innovation Services in TU Dublin. He is also Dean of the Graduate Research School with leadership responsibility for research support, technology transfer, incubation and enterprise development services. Professor O'Neill was formerly Head of the School of Media in DIT and Head of Research in the College of Arts and Tourism.

John Lynch • BSc (Pharm), MSc, M.P.S.I, Director of Compliance, HPRA

John Lynch is responsible for the inspection, licensing, market compliance and enforcement activities in HPRA. He qualified as a pharmacist from University College Dublin in 1977 and became a member of the Pharmaceutical Society of Ireland the following year. In 1980 he graduated from Trinity College Dublin with an MSc. in Pharmacognosy. From 1980 to 1987 he worked with Ricesteele & Co. in product development, quality control and quality assurance. In 1987 he joined the National Drugs Advisory Board (NDAB) as a GMP / GDP inspector and in 1996 became Director of Inspection when the IMB succeeded the NDAB. With the addition of further activities and the reorganisation of the department in 2005, his job title was changed to Director of Compliance.

Frank Hallinan, PhD, UCC, Founder-Owner Quality Systems Support

Professor Frank Hallinan is a biopharmaceutical operations expert with many years industry and Regulatory Agency experience. He is the founder-owner of Quality System Support, a consultancy service focused on providing support to pharmaceutical companies in the Quality Systems area. Frank graduated in Biochemistry from University College Cork, Ireland and received his PhD from the University of Southampton, UK. After some years in biomedical research Frank worked with Schering-Plough in development, quality and regulatory functions for over eleven years. He was CEO of the Irish Medicines Board from 1998-2002 during which period he was responsible for a number of new developments within the Agency including overseeing the Agency taking responsibility as national competent authority for medical devices. He joined Wyeth Biopharma in 2002 to head up the Quality Unit at their Grangecastle facility and subsequently worked in Pfizer Corporate Quality in Collegeville, PA where he was SVP. Subsequently he was Global Head of Quality with Jazz Pharmaceuticals. He founded Quality System Support in 2012.

Richard L. Friedman • BSc, MSc, Deputy Director, Science and Regulatory Policy, CDER, FDA

Richard (Rick) Friedman is the Deputy Director, Science and Regulatory Policy, Office of Manufacturing and Product Quality, which is part of the compliance office in FDA's Centre for Drug Evaluation and Research (CDER). In this position he is responsible for oversight of case reviews related to drug manufacturing quality to assure scientific and risk-based decisions. This position includes review of regulatory action recommendations regarding inspections and manufacturing site acceptability, and promoting sound regulatory policy development. Mr Friedman joined FDA in 1990 and his positions have included New Jersey District Drug Specialist, CDER Senior Compliance Officer, Team Leader of Guidance & Policy, Associate Director, and Division Director. Mr. Friedman has authored several publications on topics including sterile drugs and quality systems. Mr. Friedman has been an adjunct faculty member of Temple University School of Pharmacy in their QA/RA graduate programme since 2003. Prior to joining FDA, Mr. Friedman worked in the toxicology research division of Parke-Davis.

Kevin O'Donnell • PhD, Market Compliance Manager HPRA

Dr Kevin O'Donnell is the Market Compliance Manager at the Irish Health Products Regulatory Authority. He is responsible for a number of compliance-related and market-surveillance programmes at HPRA, such as the quality defect and recall programme and its sampling and analysis activities. Kevin is also a senior GMP Inspector at the HPRA. He obtained his PhD in the field of Quality Risk Management from the Dublin Institute of Technology in 2008.

Hal Baseman • BSc, MBA, Chief Operating Officer ValSource LLC

Hal Baseman is Chief Operating Officer and a Principal at Valsource and Concordia Valsource LLC. He has over 40 years' experience in pharmaceutical operations, validation, and regulatory compliance. He has held positions as the Chair of the PDA (Parenteral Drug Association) Board of Directors, the Co-Chair of the PDA Science Advisory Board, the Co-Leader of the PDA Aseptic Processing Points to Consider Task Force and the Co-Leader of the PDA Process Validation Interest Group, Co-Chair of PDA Technical Reports 22 (Aseptic Process Simulations), 44 (QRM for Aseptic Processing), and 60 (Process Validation), as well as a long-time member of the PDA Training Research Institute faculty. Hal holds an MBA in Management from LaSalle University and a BSc. in Biology from Ursinus College.

Martine Nolan • BSc, MSc, Head of Quality Kiadis Pharma

Martine Nolan is Head of Quality Kiadis Pharma, a clinical stage biopharmaceutical company based in Amsterdam, Netherlands. Previously she worked with Amgen in an EU-based regional role as Quality Head for the ADL manufacturing site in Dublin and the ABR packaging and distribution site in Breda, Netherlands. Martine originally joined Amgen in 2006 as Senior Manager Validation in Amgen Technology Ireland, Cork, Ireland. Upon the cessation of this project in 2007 Martine moved to the Amgen Breda facility in Netherlands where she took on a variety of roles of increasing responsibility within Operations Distribution Quality. Martine led the establishment of the International Quality function as part of Amgen's International Expansion whereby she was responsible for quality oversight in the Emerging Markets- Middle East, Africa, Turkey, Russia, Central Eastern Europe, Latin America and Mexico; before taking on responsibility for Quality in the EU, Australia and New Zealand. In 2012 Martine continued to grow her international experience by taking on an assignment in Istanbul, Turkey where she was responsible initially for the integration of the Amgen owned Mustafa Nevzat Ilac API and Drug Product manufacturing plants into the Amgen Quality Network, before taking on the role of Executive Director TMEA Regional Quality which included direct responsibility for Distribution Quality of Amgen products within the region and the function of MN Site Quality Head.

Barry Heavey • PhD, Director Life Science Practice Accenture

Dr Barry Heavey leads Accenture's life science practice in Ireland, with particular focus on digitalisation of manufacturing and quality. He was formerly head of Life Sciences in IDA Ireland and a board member of the National Institute for Bioprocessing Research and Training (NIBRT). Barry has a PhD in Genetics from the University of Vienna and an MBA from Edinburgh University.

Luke Kiernan • BSc, MSc, Technical Services Director Innopharma Labs

Luke Kiernan is Director of Technical Services, at Innopharma Labs. Luke's career in the pharmaceutical industry spans over 25 years with Elan, Gerard Laboratories, BioAnalytical Laboratories, Wyeth and Pfizer. Luke has held various management roles in Validation, Technical Services, Process Development, Regulatory Affairs, Analytical Method Development, Quality Control and Quality Assurance. Throughout his career he has gained extensive experience in all aspects of the validation lifecycle, six sigma methodology for problem-solving, process improvement, technical transfers, analytical method development and validation, regulatory affairs, change management, QRM and Quality Management. Luke holds an MSc in Instrumental Method of Analysis from DCU and is currently pursuing a PhD with PRST at TU Dublin.

Martin Lipa • BSc, MSc, Executive Director Merck Manufacturing Division

Martin (Marty) Lipa is an Executive Director in Merck Manufacturing Division (MMD) where he leads the *Knowledge Management Center of Excellence*. In his current role Marty is responsible for a holistic KM Strategy addressing standardised KM approaches as well as enabling elements of people, process and technology. Marty has over 10 years of KM experience, and related experience as a Certified Lean Six-Sigma Black Belt and in transformational change management. Prior to working his KM role, Marty has experience in various engineering roles, Technical Operations, shop floor automation, new GxP facility start-up and Information Technology at sites in the US, U.K., Ireland and Singapore. Marty is an active member of the KM community and is a regularly invited speaker on KM. Marty has published several industry specific works, most recently as contributing editor to 'A Lifecycle Approach to Knowledge Excellence in the Biopharmaceutical Industry' (2017), as well as works in *ISPE Pharmaceutical Engineering* and *OD Practitioner*.

Marty is currently pursuing a PhD at the Technological University Dublin with a focus on Knowledge Management as an enabler of product and process understanding, with a specific focus on Technology Transfer.

Paige Kane • PhD, Director MSD

Dr Paige Kane graduated with a PhD from the DIT in October 2018 on the topic of the ICH Q10 Enabler of Knowledge Management. Paige is employed full-time with MSD as a Director in the MMD Knowledge Management Center of Excellence, joining in 2016 from Pfizer (Wyeth/Genetics Institute). She is a regular industry speaker with over 25 years' experience in biopharmaceuticals, spending the past 11 years leading KM programmes and approaches for the Pharmaceutical Industry. Prior to KM she led Quality Systems Groups (Change Control, Document Management, Computer/Equipment Validation and Data Integrity) and new facility start-ups in the US and Ireland, with prior compliance experience across GLP/GCP/GMP areas. Dr Kane is a co-editor of, and contributor to, 'A Lifecycle Approach to Knowledge Excellence in the Biopharmaceutical Industry' (2017).

Ghada Haddad • BSc, MSc, Executive Director MSD

Ghada Haddad is the Executive Director, Global cGMP Compliance and Auditing Organisation at MSD. She holds a chemistry degree and an MBA. She has over 18 years of experience working in the Biotech and Pharmaceutical industries in the areas of Quality Risk Management (QRM), Quality Systems and Regulatory, including research, management (people and projects), process development, auditing, regulatory agency inspection, change control and validation. Her experience in Quality Risk Management (QRM) includes deploying global QRM programmes, training others in the concepts and tools, and on integration of QRM into Quality Systems. She is also a faculty member for PDA's Training and Research Institute and a Science Advisory Board member. Ghada is currently pursuing a PhD at the Technological University Dublin with a focus on developing a Competency Framework for QRM.

Eamonn McGowran • BSc, MSc, QA & Regulatory Manager Klox Tech

Eamonn McGowran is a graduate of Dublin City University with a BSc in Biotechnology and an MSc in Plant Biotechnology. Eamonn is a highly knowledgeable regulatory and quality professional with over 20 years' experience. He has worked within the pharmaceutical, bio-pharmaceutical, medical device, food and cosmetics sectors where he has developed a wide understanding of global regulatory and quality needs to gain access to markets for both large and small organisations. Through interactions with university researchers, Eamonn has developed a strong interest in the incorporation of Regulatory Science understanding at the early stages of innovation. He is undertaking a PhD in TU Dublin exploring the early adoption of Regulatory Science in the drug development lifecycle.

Prof. Anne Greene • Head, Pharmaceutical Regulatory Science Team (PRST), TU Dublin

Anne Greene leads the Pharmaceutical Regulatory Science Team (PRST) in TU Dublin, where she is also a senior lecturer and director of the several MSc. and BSc. Pharmaceutical Programmes.

Prior to embarking on an academic career, Anne worked at a senior level for several years in the pharmaceutical sector in Validation and Technical Management roles. Anne has a PhD in Synthetic Organic Chemistry from University College Dublin, and is currently on the advisory committee of the Irish Chapter of PDA. Anne is also on the Board of Directors of Regulatory Science Ireland (RSI) and is chair of the Coporate Development Committee.

Dr Anne Murphy • Higher Education Policy Research Unit, TU Dublin

Anne Murphy is an Emeritus Research Fellow with a long career in education as a teacher, academic development practitioner, research supervisor and project manager, specialising in recent years in recognition of prior learning, work-based learning, qualifications frameworks development and TVET systems in Europe and in Serbia, Turkey, Macedonia, Kosovo, Afghanistan, Uzbekistan, Kazakhstan and Malaysia. She founded the first DIT open access, online journal in 2003, was instrumental in developing the concept of the DIT Academic Press and was a long term reviewer for Emerald Publishing. She is currently a CORU public interest panel member for regulation of qualifications in the health and social care professions in Ireland.

Dr Elaine Harris • School of Chemical and Pharmaceutical Sciences, TU Dublin

Elaine Harris is an assistant lecturer at the School of Chemical and Pharmaceutical Sciences in TU Dublin and runs a consultancy company, Innovation21. Her primary research interest is innovation in Regulatory Sciences and she is a member of TU Dublin's PRST. She also currently works at Invent, Dublin City University where she is the Intellectual Property Manager for the Fraunhofer Project Centre for Embedded Bioanalytical Systems (FPC@ DCU).

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Part 1: Introductory Remarks

1.1 The significance of facilitating open access to research in Regulatory Science

Brian O'Neill, Director of Research and Enterprise, Dean of Graduate Research School, TU Dublin

It is a real pleasure to be associated with this monograph based on the TU Dublin seminar on 4 April 2019 *An Audience with Regulators, Academia and Industry* organised by the School of Chemical and Pharmaceutical Sciences, the Health Products Regulatory Authority and Regulatory Science Ireland. TU Dublin highly values its associations with the pharmaceutical sector in general and with the emerging field of Regulatory Science in particular. We are proud to be involved in the dialogue evident in this monograph among global thought-leaders, practitioners and researchers in this important field.

As you know, TU Dublin is a new nomenclature and a new legal entity as a university building on its long traditions of teaching and research in the city. We are now the largest higher education institution in the state with *circa* 29,000 students and continuing our collaborations with industry, the labour market and civic society.

In TU Dublin we take pride in the research and scholarship being undertaken by our staff and postgraduate students in the areas of Pharmaceutical Regulatory Science which is at the forefront of our mission as a forward-thinking, progressive new university on both national and global landscapes.

The topics in this monograph around innovations in regulation of health products manufacturing and the benefits of science to society could not be closer to what we as a university are committed to continue doing i.e. fostering and supporting dialogue, making research knowledge available, and actively dissemination knowledge to the wider society so that members of the public can become involved in decision-making that affects their lives.

Because the key economic sector in Ireland – pharmaceutical, financial services and ICTs – are vital to our future, our eyes are constantly on global industry and on the important decision-making that informs it. We as a university very much want to be part of facilitated discussions towards decision-making. This is very much my understanding of the context for the work that is presented in this monograph, the second in the series.

On my own behalf, and on behalf of President David FitzPatrick, I sincerely support and commend this worthy publication.

1.2 The importance of research into QRM and KM for patient safety

John Lynch, Director of Compliance, HPRA

This monograph contains important contributions to knowledge for the regulatory science sector, for regulators themselves, for industry, and for academia. Following on from the seminar in October 2018 and the first monograph published thereafter, we are delighted that a second monograph has resulted from the second seminar of April 2019. We are also delighted that TU Dublin has brought together some of the world's thought-leaders to discuss the real value that can be delivered by practicing effective quality risk management, not just as a compliance requirement, or as an aid to business, but most importantly as a means to reduce risk to patients, both human and animal, from the biopharmaceutical products the industry produces.

Regarding quality risk management, it is heavily used by regulators and industry alike. As a regulator, we use it in a wide range of areas: in our planning and conduct of GXP inspections, in marketing, and in assessment strategies around applications to place medicines on the market. We also use it in decision-making around quality defects and recalls, in the design of surveillance programmes, in pharmacovigilance work, and in a variety of other areas.

Now I will make a rare admission of fallibility: *we are still learning to apply QRM principles and tools really well!* QRM is now widely embedded in the GMPs of the EU and other regions and industry has certainly embraced it. Fifteen years ago we would rarely come across formal risk assessment on inspection. Some practices might not have been very good and may have had a pre-determined outcome from the risk assessment exercise, but not in all cases. Nowadays, risk assessments are very widely applied and are of far better quality. That said, there is still some way to go to ensure that our work is paying dividends for patients, both human and animal.

That brings me to the second theme of this monograph: knowledge management. I think it is reasonable to say that collectively we are not so advanced in the area of formal knowledge management. Hence it is an area in which we all have a keen interest.

Speaking about knowledge management and quality risk management, the integration of QRM and KM in management systems in an organisation is a key factor in enabling effective QRM in order that decision-makers have access to the right information when and where they need it. Indeed, it is a welcome sign that a large part of this monograph is about knowledge management.

So, this monograph righty focuses on the roles both QRM and KM can play in ensuring medicinal product safety for patients in the twenty-first century, which is in line with the vision of ICH Q10.

1.3 Introduction to Regulatory Science Ireland (RSI)

Frank Hallinan, Founder-Owner Quality Systems Support

Regulatory Science Ireland (RSI) is an initiative that Technological University Dublin (TU Dublin), University College Cork (UCC) and a number of state bodies have been involved in for a number of years now. We established RSI in 2012 to a large extent based on the initiative of the US Food and Drugs Agency (FDA) in this area. So, let me start by explaining a little about what Regulatory Science actually is. The US FDA was the first organisation to use this term. They defined it as "*the science of developing new tools, standards and approaches to assess the safety, quality and performance of drug products*." So, to us it is about taking the methodology for approving drug products and looking at it in an objective, data-driven way in terms of the way it is being done, as opposed to simply continuing to do it as it has been done in the past. The EMA came up with a reasonably similar definition and has developed a strategic plan in this area. So, this is a real, live topic in the field of regulation of medicines at this particular point in time. Therefore, when we set up RSI we felt it was important that we would have an initiative in this area in Ireland.

The reason for Regulatory Science as a concept at this point in time is perhaps because the FDA pointed out in 2011 that the challenges of product development and globalisation underscore the critical importance of modernising and advancing regulatory science to match the advances in basic and applied science and technology.

So, the sciences generally are moving forward very quickly, and therefore the sciences concerned with regulation need to move forward in parallel with that. The then FDA Commissioner, Dr Scott Gottlieb commented in 2017 on the occasion of FDA approval of the first gene therapy product Luxturna in the US that there were more than six-hundred INDs related to gene therapy products with the Agency at that particular time, and that it is estimated by experts in MIT that about forty of these proposed products might have won approval by 2022 from a current list of 932 pipeline candidates, with 45% of these products related to treatments for cancer.

Based on this level of activity it seems likely that the world of biopharmaceuticals is changing quite radically even as we speak at this symposium.

Consequently, we need to ensure that the regulatory paradigm and regulatory approach keep up to date with current and possible future changes. In that regard, the type of work and research contained in this monograph from TU Dublin is a very good example of the activities that need to be done both to up-skill people and to transfer knowledge into Ireland Inc. so that we continue to be at the forefront in this area.

Regulatory Science has evolved since the concept was first put forward in 2010 by the FDA for the purpose of advancing science for public health. The 2011 document from the FDA built on the original concept.

The EMA 2012 document and the Roadmap to Regulatory Science currently under discussion are pan-European examples of the concept.

One of the initiatives that came out of the FDA was the establishment of the so-called CERSIs - Centres for Excellence in Regulatory Science and Innovation - in various universities in the US funded by the FDA.

While we do not yet have any such Centres in Ireland at this point in time funded by the Government or any national Agency, we in RSI would certainly welcome and encourage such an initiative. However, our RSI initiative is an attempt by those of us who are involved in the field to try to develop that type of approach in the future.

So, what is Regulatory Science Ireland and what is its particular mission?

RSI is a network of interested parties from academia, the pharmaceutical industry, the medical device industry, and various governmental agencies involved in the area of bio-pharmaceuticals. All of us collectively are committed to the development of an integrated Irish response to the global Regulatory Science effort. We are looking in particular at the fields of research, education and training, and knowledge-sharing. These are the particular areas of our focused interest.

We hope through RSI to provide relevant research, training and communication that facilitate the Irish contribution to an effective response to the increasing complexity of health products and their associated regulatory systems that creates a cohort of Irish-based regulatory science experts – not *regulatory affairs* experts, but *regulatory science* experts, who further strengthen Ireland's attractiveness as a location for people in this particular sector, and finally that it is patient-focused. Everything comes back at-the-end-of-the-day to the patient. So, it ties in as well with a quality culture in the broadest possible sense.

This is how RSI works. The Directors create an annual workplan with an emphasis on the particular focus areas mentioned earlier i.e. research, education and training, and knowledge-sharing.

One of the biggest initiatives we had so far is a project in the area of biosimilars. This was set up to raise awareness of the special qualities of biological products, particularly biosimilars, in order to understand the level of awareness among patients and healthcare providers so that we can contribute to best practices in that particular area. That research has been completed and a number of publications have arisen from it.

So, what is the future?

RSI is a company now, limited by guarantee, with a company registration number and so on.

We want to build on the successes we have had to date. We want to maintain and extend our network of stakeholders, and we want to have it regarded as a European Centre of Excellence to support the important place that Ireland Inc. has in the business of healthcare products manufacturing at this particular point in time.

So, really the fundamental purpose of my contribution to this monograph is to assist in general understanding and particular sector support for RSI and its mission. Generally, it is difficult to explain the mission of RSI to the sector as the sector itself is normally more focused on today's problems than on possible future problems and solutions. So, this monograph is an opportunity to explain RSI and its mission to a wide readership in the sector.

RSI welcomes contributions and advice from the sector at any time through its contact points in TU Dublin and University College Cork.

Part 2: Regulatory Matters

2.1 Demonstrating the Effectiveness of the Pharmaceutical Quality System from a Quality Risk Management Perspective

Kevin O Donnell, Market Compliance Manager HPRA

Introduction

As regulators with the Health Products Regulatory Authority (HPRA) my colleagues and I deal with various problem issues that result in quality defects and recalls of medicines every year. Indeed, in 2018 we investigated approximately 1050 reports of quality defects, and these resulted in 204 recalls of medicines in Ireland. Each of these issues presented risks to patients (and sometimes to animals, in the case of veterinary medicines) which were unintended and unanticipated, and this called into doubt whether the manufacturing processes had truly been validated with QRM principles in mind, as required by the GMPs.

The quality defects area is of relevance to my talk today, because it directly relates to the effectiveness of the manufacturer's pharmaceutical quality system in terms of quality risk management. Truly effective pharmaceutical quality systems from a risk perspective can be expected to provide a high degree of assurance that the batches released by that manufacturer will not present risks to patients and animals via the presence of quality defects in those batches.

ICH Q10 – Annex 1

Reflecting on ICH Q10, published in 2008, which describes the ICH model for the Pharmaceutical Quality System (1), is a good place to begin. In the last decade since its publication ICH Q10 has been widely discussed by the Industry. However, while the document itself is well known, there is little evidence that Annex 1, which describes *Potential Opportunities to Enhance Science and Risk Based Regulatory Approaches*, has been considered to any meaningful extent.

Table 1 opposite is presented in Annex 1 of ICH Q10.

SCENARIO	POTENTIAL OPPORTUNITY
1. Comply with GMPs	Compliance - status quo
2. Demonstrate effective pharmaceutical quality system, including effective use of quality risk management principles (e.g., ICH Q9 and ICH Q10).	Opportunity to: • increase use of risk based approaches for regulatory inspections.
3. Demonstrate product and process understanding, including effective use of quality risk management principles (e.g., ICH Q8 and ICH Q9).	Opportunity to: • facilitate science based pharmaceutical quality assessment; • enable innovative approaches to process validation; • establish real-time release mechanisms.
4. Demonstrate effective pharmaceutical quality system and product and process understanding, including the use of quality risk management principles (e.g., ICH Q8, ICH Q9 and ICH Q1O).	Opportunity to: • increase use of risk based approaches for regulatory inspections; • facilitate science based pharmaceutical quality assessment; • optimise science and risk based post-approval change processes to maximise benefits from innovation and continual improvement; • enable innovative approaches to process validation; • establish real-time release mechanisms.

Table 1

The first scenario described in the table is that, when companies just comply with the GMPs, there is little opportunity for those companies to access regulatory relief from regulators. However, when companies apply the principles and concepts outlined in ICH Q8 (Pharmaceutical Development) (2), ICH Q9 (Quality Risk Management) (3) and ICH Q10 (Pharmaceutical Quality System), there are opportunities open to them in relation to science and risk-based regulatory approaches, which constitute various forms of regulatory relief, such as reduced frequency and scope risk-based inspections, innovative approaches to process validation, and flexibility in relation to post-approval change management.

A key to this relief is demonstrating the effectiveness of the Pharmaceutical Quality System, as outlined in the ICH Q10 annex. But in my experience, this key aspect of ICH Q10 appears to be poorly understood and not discussed very often.

As regulators, we apply the concepts outlined in ICH Q10 within our agencies, as demonstrated by the following 3 examples:

Example 1: In relation to GMP inspection planning:

Many regulatory agencies, including the HPRA, apply QRM principles and tools when planning GMP inspections. Formal risk ratings are applied to sites that help inform the frequencies of inspections and their scope. At the HPRA, these ratings are derived from the application of a customised version of a PIC/S risk-based GMP inspection planning tool (4, 5) which the HPRA was heavily involved in developing together with inspectors from other agencies. This tool allows for science-based risk ratings to be applied to manufacturing sites – it considers complexity, criticality and compliance-related risk factors when risk assessing sites, and the result is both increased and reduced frequency inspections, as well as a risk-based inspection scope being developed for the next inspection at each site.

Example 2: In relation to risk-based surveillance testing by medicines agencies and Official Medicines Control Laboratories (OMCLs):

Customised and science-based QRM tools have been developed to support the design and execution of risk-based independent surveillance activities performed by competent authorities and their OMCLs. This is where companies and products that score high in risk are more likely to be subjected to surveillance work than others.

Example 3: In relation to the assessment of Marketing Authorisations and their related applications by Competent Authorities:

Risk-based approaches are also applied by assessors when assessing Marketing Authorisation applications, and customised QRM tools have been developed for this work.

Time for Reflection…

While the examples above demonstrate three quite different applications of science and risk-based approaches, it is interesting to note that they have all been regulator-driven, and indeed, regulator initiated. We are generally not seeing companies approach regulators with data which make a case for being granted regulatory relief in these or other areas. It would be interesting to know how many pharmaceutical companies have demonstrated sufficient effectiveness in their Pharmaceutical Quality System to the degree where their regulators have agreed to give them some form of regulatory relief based on science and risk? While data are not readily available on this, it is, from my own experience, likely to be few in number.

It seems that most individual companies do not proactively make the case for receiving risk-based regulatory oversight from their regulators to any meaningful extent, and perhaps there is a lack of proactive initiatives in the area by the industry generally. While regulators do need to be somewhat conservative by nature when it comes to risk, there are opportunities for the industry, via ICH Q8, Q9 and Q10, to access more risk-based approaches by regulators, when the effectiveness of their pharmaceutical quality systems has been demonstrated.

It is timely to discuss this at this time, given the pending finalisation of the ICH Q12 guideline entitled '**Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management**" (6). This guideline is anticipated to be finalised in 2019.

ICH Q12 & Post-approval Change Management

A large part of ICH Q12 focusses on post-approval CMC change management, and it sets out new ways to manage post-approval changes based on established conditions and risk considerations. It places a strong emphasis on the need for an effective pharmaceutical quality system to be in place, and it lists various principles of change management that will need to be complied with in order to access the regulatory flexibility that is envisioned.

It also discusses the role that knowledge management has in relation to triggering post-approval changes that may or may not require prior approval by regulators, and the connection between Knowledge Management and Change Management is presented in a diagram that is reproduced below in **Figure 1**.

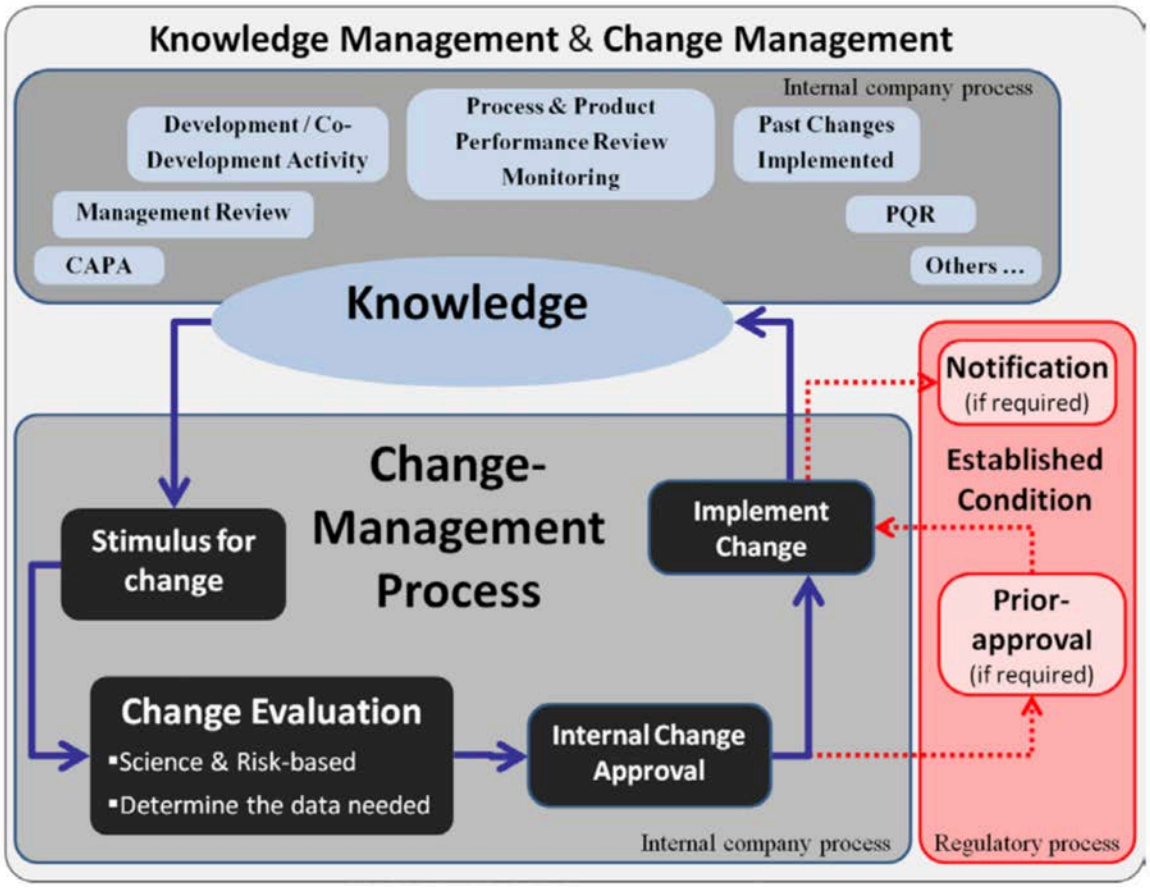

Figure 1

Focusing on the pink section of this diagram on the righthand side, the vision of ICH Q12 is that companies may be allowed to make certain CMC changes with reduced regulatory oversight when they meet certain pre-conditions, and demonstrating the effectiveness of the PQS is one such condition. This all can be linked back to Appendix 1 of ICH Q10, the premise of which is that, where a company applies the principles and concepts of ICH Q8(R1), ICH Q9 and ICH Q10 and demonstrates the effectiveness of its PQS, it may be eligible for some degree of regulatory relief, including relief in relation to post-approval change management.

Demonstrating effective PQS

It is important to note, however, that demonstrating the effectiveness of the PQS is not just an ICH Q10 concept; it is also a core expectation of the EU GMPs (7). The following are relevant extracts from Chapter 1 of the EU GMP guide, which sets out the expectations in relation to the PQS.

- **Principle**: To achieve this quality objective reliably there must be a comprehensively designed and correctly implemented PQS incorporating GMP and QRM. It should be fully documented and its effectiveness monitored.
- **Section 1.3**: While some aspects of [the PQS] can be company-wide and others site-specific, the effectiveness of the system is normally demonstrated at the site level.
- **Section 1.4:** A PQS appropriate for the manufacture of medicinal products should ensure:
  xvii) There is a process for self-inspection and/or quality audit, which regularly appraises the ***effectiveness*** *and applicability of the PQS.*
- **Section 1.5**: Senior management has the ultimate responsibility to ensure an effective PQS is in place…

This emphasis in the GMPs on demonstrating that an effective PQS is in place leads one to consider how this may be achieved at a practical level. There is currently little guidance available on this, and the HPRA is interested in exploring this topic. At a simplistic level, one might wonder if it involves some of the following activities:

- *Is it about displaying satisfactory CAPA and other metrics data on a chart in a corridor in a manufacturing plant? (Such charts are now very common in many manufacturing sites.)*
- *Is it about signing off Management Review reports that conclude that everything is in control?*
- *Is it about when all PQRs conclude that the processes are operating consistently?*
- *Is it when there is a low level of non-compliance detected via Self Inspections?*
- *Is it about Corporate Audits resulting in good site ratings?*
- *Is it when no Critical or Major deficiencies were issued at the last regulatory inspection?*
- *Or is it simply about a having a GMP Cert?*

I think that demonstrating the effectiveness of the PQS is more complex than simply doing the above activities. In order to tackle this problem, the HPRA has decided to focus attention on just a sub-set of PQS effectiveness for now, and this relates to PQS effectiveness from the perspective of quality risk management.

Demonstrating PQS Effectiveness from a QRM Perspective

This is a useful approach to take, because so much of the GMPs now rely on effective QRM activities. This is evidenced by the fact that over the last 10 years or so, the EU GMP guide (7) has been significantly revised to incorporate QRM principles and references to risk assessment in several chapters and annexes, such as Chapters 1, 3, 5 and 8, and Annexes 1, 2, 11, 15, 16 and 17.) For example, Annex 15, on Qualification and Validation, now states:

> *'A quality risk management approach should be applied throughout the lifecycle of a medicinal product. As part of a quality risk management system, decisions on the scope and extent of qualification and validation should be based on a justified and documented risk assessment of the facilities, equipment, utilities and processes.'*

> *'The way in which risk assessments are used to support qualification and validation activates should be clearly documented.'*

In addition, it is anticipated that the successful implementation of ICH Q12 will rely heavily on QRM, and the current draft carries this wording:

> *'An effective change management system is one that ...requires a science and data-based risk assessment and risk-categorisation of the proposed change, including the management of risk in the event the proposed changed is not implemented.'*

When trying to understand what PQS effectiveness means from the perspective of QRM, one might consider the following:

- Does it mean that all potential quality-related risks posed to patients and animals are rendered low, via risk control or mitigation?
- Does it mean that the QRM activities at a site are seen to be working correctly?
- Does it mean that a site's risk registers show only green risks?
- Might it mean that the objectives of all QRM activities are consistently met? (*What are the typical objectives of QRM activities at sites?*).

Clearly, there is more to do in this area if we are to truly understand how PQS effectiveness might be demonstrated from the perspective of QRM. And in response to this, the HPRA has developed a model that might serve as a starting point or further work in this area. This is described below.

A Potential Model for Demonstrating PQS Effectiveness from a QRM Perspective

In order to develop an approach for *demonstrating PQS effectiveness* from a QRM perspective, the following is one suggested model that may serve as the basis for future work in this area. It is designed around the principles and guidance of ICH Q9 and Q10, and it is based on three key components:

- *The successful integration of QRM with the four key elements of the PQS as set out in ICH Q10:*
  - » *Process Performance and Product Quality Monitoring Performance*
  - » *Change Management*
  - » *Corrective and Preventative Action (CAPA)*
  - » *Management Review of Process Performance and Product Quality*
  - » *The first principle of QRM as per ICH Q9*
  - » *The second principle of QRM as per ICH Q9*

The model can be visualised as shown in **Figure 2** below:

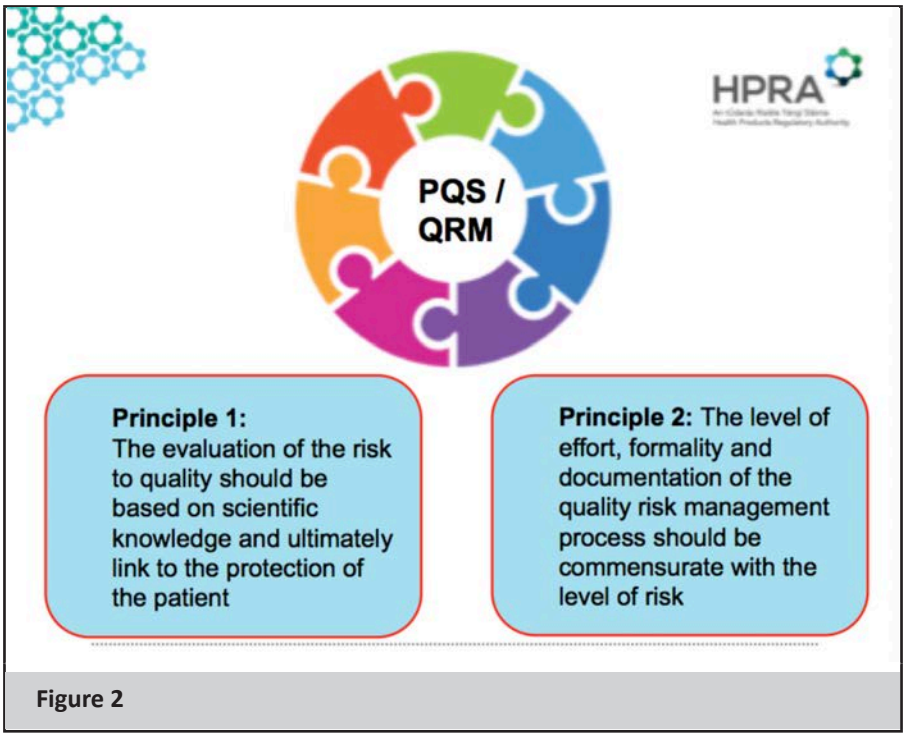

Figure 2

A Potential Model for Demonstrating Pharmaceutical Quality System Effectiveness from a QRM perspective

Reflecting the concepts and principles of ICH Q9 and ICH Q10

The Pharmaceutical Quality System (PQS) can be considered effective from a Quality Risk Management (QRM) perspective when one can show the following:

1. QRM is integrated across the four key elements of the PQS as per ICH Q10

The Process Performance and Product Quality Monitoring Performance System: for example;

- The control strategy has been informed by an understanding of process and other risks to Critical Quality Attributes (CQAs), and it can be directly expressed in terms of risk control.
- Risk assessment and risk control activities have informed the design of Qualification and Validation protocols.
- The system generates verifiable data that demonstrates the state of control at any point in time as well as indicating areas for improvement to reduce variability.
- The monitoring system provides empirical evidence that the risks of producing out-of-specification / defective / non-compliant batches are under adequate control.

The Change Management System: for example;

- All Change Controls deliver demonstrated risk reductions or they ensure there is no increased risk to product quality.
- When using QRM to evaluate proposed changes, the level of testing performed during and after the change control is commensurate with the level of risk.
- The system drives innovation and continual improvement which lead to reduced risks.

The Corrective and Preventative Action (CAPA) System: for example;

- There is a high degree of assurance that CAPAs deliver the required level of risk reduction with respect to the root causes and consequences of deviations, complaints, non-compliances, audit findings, and other issues.
- The system emphasises CAPAs that focus on prevention rather than detection.

The Management Review of Process Performance and Product Quality element: for example;

- Management Reviews lead to improvements in manufacturing processes and products, resulting in risk reductions.
- They lead to the provision of training and/or a realignment of resources where required, resulting in adequate risk control and in the necessary QRM competencies being in place.

- They lead to the capture and dissemination of process and product knowledge, facilitating more robust risk assessments.
- The Management Review system verifies that the four elements of QRM as per ICH Q9 (Risk Assessment, Risk Control, Risk Communication and Risk Review) are in operation to the required standard and that they feed into decision making.
- The self-inspection programme is designed taking process complexity, criticality and risk into account and it generates data that confirms that the state of control is maintained.

2. *Scientific knowledge is applied in all risk assessments*

- Risk Assessment tools or approaches result in the scientific measurement (or at least reliable estimation) of risks, both before and after risk mitigation.
- The role that GMP controls have with respect to the probability of occurrence, severity and detection of hazards / negative events is documented (when these three factors are rated or considered during risk assessment and risk control exercises).
- The factors that can lead to subjectivity and uncertainty (e.g. human heuristics) in the outputs from risk assessments are addressed by science-based countermeasures.
- Risk control strategies are predominantly based on prevention rather than detection.

3. *The evaluation of risk to product quality ultimately leads to patient protection*

- Meaningful risk reduction is achieved for patients as a result of risk assessment and control activities that relate to product quality.
- One can measure (or estimate) product quality risk levels and residual risk levels as they relate to patients.

4. *The level of effort is always commensurate with the level of risk*

- ***Question***: How can companies demonstrate that the level of effort which was applied was sufficient?
- Is it about the degree of rigour applied during a risk assessment?
- Is it about reflecting complexity? The more complex the subject matter, the more rigorous the risk assessment needs to be?

(Note: This part warrants further research work.)

5. The level of documentation is always commensurate with the level of risk

- ***Question***: How can this be demonstrated?
- In a complex manufacturing process that is under a good state of control, the risks of producing a defective and harmful batch may be low, so is a low level of documentation of QRM activities sufficient here?

(Note: This part warrants further research work.)

6. The level of formality is always commensurate with the level of risk

- Question: What is formality in QRM?
- Is this about using tools (or not using tools)?
- Is it about how much rigour is applied?

(Note: This part warrants further research work.)

Conclusion

The model presented in this paper is intended as a starting point for discussion and dialogue on how to demonstrate the effectiveness of a site's PQS from a QRM perspective. While the model is relatively simple in structure, it has been designed around the concepts and guidance of ICH Q9 and ICH Q10, and it incorporates a number of key areas of importance, including the following:

- Proactive approaches to QRM (e.g. Change Management, Qualification & Validation activities, etc.)
- Reactive approaches to QRM (e.g. CAPA activities)
- Product-related monitoring activities
- Process-related monitoring activities
- Management activities
- The need for good science
- Effort, Formality and Documentation-related considerations
- And importantly, patient protection.

It is hoped that this model may serve as the basis for additional work in this area over the next year or two, so that practical solutions may be developed by the pharmaceutical industry as individual sites may seek to demonstrate the effectiveness of their PQS in relation to QRM.

In relation to the question of how can companies get to the stage where they are able to access the regulatory flexibility foreseen by Annex 1 in ICH Q10, perhaps this model may serve as a useful place starting point.

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Part 3: Industry Matters

3.1 Innovative Aseptic Process Intervention - Risk Assessment and Evaluation

A Critical Thinking Approach to Improving Sterile Product Manufacturing

Hal Baseman, Chief Operating Officer, ValSource LLC

In this paper the author, Hal Baseman, presents, through case studies, some innovative approaches to risk management ***of aseptic processing***, using risk intervention in particular.

In his opinion, the purpose of Quality Risk Management (QRM) is to enable process improvement. The object is not just to identify risk, but to mitigate the risk by improving the process. In his vast experience of over 40 years in this industry he believes we do not carry out critical thinking like other industries do in order to improve their processes. As presented by Baseman, this is an interesting time for QRM, as it is getting the attention of the regulators. This is further reflected in the papers and Q&A in this monograph. This dynamic presents a great opportunity for industry to improve processes because, if regulators are expecting us to use QRM and risk-based thinking, we should be able to use risk-based thinking to justify approaches to process improvement. Indeed, the opportunity is here for industry to replace outdated and ineffective traditional methods regarding process and contamination control, with much needed, more effective and innovative approaches. If companies are being asked to use QRM principles to justify decisions related to given approaches, then competent authorities should accept alternate approaches that are based on sound risk-based decision-making.

Aseptic process improvement

Baseman notes that aseptic processing is a particular challenging area for QRM, as the process tends to be complex and variable. While thankfully we only have rare failure events, this means it is not easy to discover correlations between what we can observe and the desired effect. It is hard to identify measurable criteria that can lead to objective risk assessment.

Focusing on people in aseptic processes is a challenge, as even with the best of intentions, people are going to be highly variable in their performance. In addition, there can be conflicting work objectives for operators. For example, one objective is to get the product out, while the other objective is to follow the rules and procedures. But in which of these objectives is the success most easily measured? This emphasises the importance of the need to establish a sense of awareness as to why these procedures are important, and the impact of not following them. To illustrate these points, Baseman present four case studies below.

CASE STUDY 1: Development of PDA TR 44 QRM for Aseptic Processes

This case study is drawn from PDA Technical Report 44 (1), which was the first technical report that PDA produced on QRM for Aseptic Processing, written in 2008, right on the heels of ICH Q9 (2). Not a lot had been written on QRM, so a diverse Taskforce of about 15-16 members, made up of a group of industry and regulatory participants, was convened to develop it.

Model Proposed by the Taskforce

The initial model the Taskforce developed was a Failure Mode and Effects Analysis (FMEA) style risk assessment type, shown in **Table 1** below.

REF #	Process Step	Failure	SEV	Cause	OCC	Current Control	DET	RPR	Risk Accepted (?)	Recommend Actions	Ranking After Actions			
											SEV	OCC	DET	RPR

Table 1: FMEA model

The model uses a 1-10 scale to measure severity, occurrence, and detection, where:

Severity (SEV):

- *Very low to no impact, 1*
- *Unimportant failure, 2-3*
- *Failure of medium importance may cause customer troubles, 4-6*
- *Critical failure, will dissatisfy customer, 7-8*
- *Extremely critical failure, 9-10.*

It should be noted that for aseptic processing, the team concluded that severity would always be high, based on the hazard being the loss of sterility or loss of sterility assurance, resulting in potential infection.

Occurrence (OCC):

- *Very low probability, 1*
- *Failure might happen, but very seldom, 2-3*
- *Failure happens from time to time, 4-6*
- *Failure happens frequently, 7-8*
- *High probability that failure happens, 9-10*

Detection (DET):

- *Failure detection is ensured 1*
- *High probability of failure detection 2-3*
- *Failure detection not sure 4-6*
- *Low probability of failure detection 7-8*
- *Failure detection is highly improbable 9-10*

This is a typical approach used in FMEA tools. However, for aseptic processing the Taskforce felt Severity (if there is a failure) is always high, so they suggested it be constantly assigned a **high value of 9-10**.

In addition, the Risk Priority Ranking (RPR) is obtained by multiplying the severity, occurrence and detection. (RPR = SEV x OCC x DET). Then, based on the number obtained, you assign a category to the risk based on the values in **Table 2** below:

1-125	Very low process risk	Category IV
126-250	Low process risk	Category IV
251-500	Moderate process risk	Category III
501-750	High process risk	Category II
751-850	Very high process risk	Category II
851-1000	Extreme-critical process risk	Category I

Table 2

The risk associated with each category is articulated in **Table 3** below:

Category I Catastrophic	A failure which can represent serious and/or unexpected product adverse experiences or serious bodily injury
Category II Critical	A failure which may cause probable unexpected product adverse experiences, severe injury or inconvenience
Category III Marginal	A failure which may cause minor injury or inconvenience, or possible product adverse experience
Category IV Minor	A failure not serious enough to cause injury or inconvenience or other product adverse experiences

Table 3

Execution of Risk Assessments by the Taskforce

The Taskforce was then subdivided into small teams, which were assigned the task of carrying out several Risk Assessments for different types of scenarios relating to aseptic processing. Some scenarios were hypothetical, while some were from volunteer facilities. Each team gave feedback of their experiences on a weekly basis, identifying what worked and what didn't work, and where modifications were needed. What started to become apparent was that: *this was not working at all!* The FMEA-like model developed was not very effective: in fact, it was failing. Here is an illustration of why that was occurring.

Imagine we are reviewing a Risk Assessment which identified a Category II or Critical level of risk. It is unlikely that one would accept that.

However, if we came to you and said that we did the Risk Assessment and came up with a Category III or Marginal level of risk, you might be able to rationalise it and accept that.

The problem is that the model has a transition point where the risk may/may not be accepted. In this case, a value of 500 is acceptable and 501 is not. What was occurring with the teams out in the field testing the model was that they spent almost all their time on the Risk Assessment arguing for each section (OCC) and (DET) over whether the number was 4, 5, or 6. If you were a risk-adverse person by nature you are arguing to 6, while if you are a risk-tolerant person by nature you are arguing to 4. Does it really matter what the number is? That doesn't change the risk: it just leads to highly subjective results. Whoever is the loudest carries the day!

So, we tried other scales. We changed the scale from 1-5, then 1-7, all even numbers, all odd number, 1-3. But that didn't fix the problem. We realised that it wasn't the numbers that were the problem, it was using numbers!

It was then that we moved away from using numbers, and started using colours. The next case study demonstrates this approach.

CASE STUDY 2: Remove the numbers and change the focus

In this Case Study we worked to develop prescriptive terms which are described in detail in TR 44(1), but can be summarised as follows:

Occurrence

- *If a failure almost always occurs it is Red*
- *If a failure almost never occurs it is Green*
- *Everything else is Yellow*

Detection

- *If detection is close to zero it is Red*
- *If detection is almost certain it is Green*
- *Ever thing else is Yellow.*

This is visualised in **Table 4** below.

		Detection		
		Low	Medium	High (It is not likely failure will be detected.)
Occurrence	High	Medium	High	High
	Medium	Medium	High	High
	Low	Low	Medium	Medium

Table 4

Again, for this case, Severity is always High. So, using a severity of 5, the options are summarised in **Table 5** overleaf.

Ranking	Risk Factors		
	Severity	*Occurrence*	*Detection*
HIGH	Severe	Often	Failure will almost certainly escape detection.
MEDIUM		Periodic	Controls may detect the existence of a process failure.
LOW		Seldom	Obvious and readily detected

Table 5

This was further expanded to develop the module shown in **Table 6** which is more of a thinking model which does not itself make the decision, but instead provides information which guides the decision.

		DETECTION		
		LOW	MEDIUM	HIGH
OCCURRENCE	HIGH	This cause is likely to occur, but when it does it will be detected. If we are certain it will be detected it is low risk, but if we are not certain then it should be a Medium Risk	This cause is likely to occur and the detection is not certain. It is a High Risk.	This cause is likely to occur and is not likely to be detected. It has a High Risk
	MEDIUM	This cause could occur, but if it did it would be detected. Depending on the frequency of occurrence and the confidence in the detection, it is a Low or a Medium Risk.	This cause could occur and it could be detected. Depending on our confidence in the detection its risk would be Medium or High	The cause may occur and it will not be detected. The Risk is High.
	LOW	This cause is not likely to occur and if it does it will be detected. This is a Low Risk.	The cause is not likely to occur and if it did it may be detected. Depending on the frequency of occurrence and confidence in detection methods, it would be Low or Medium Risk.	The cause is not likely to occur, but if it did occur it would probably not be detected. The Risk is Medium.

Table 6

In this model there are shades of green, yellow and red. The overlap areas, with the shading merging, is the area where the assessment team had a discussion, evaluated different scenarios, and really talked about the risk, chances of occurrence, and possibility of detection.

This tool is a '*thinking person's model*' which enables the gathering of collective experiences to enable the decision. This is in contrast to the other modules shown where the tool makes the decision.

CASE STUDY 3: Simple example: Lyophilized Vial Capping

This is a simple case study to demonstrates how this works, and it focuses on a Lyophilized Vial, the manufacturing process of which is summarised in the process-flow diagram shown in **Figure 1** below. The specific manufacturing step, which is the focus of this risk assessment, is shown in yellow in the diagram, and centers around putting the cap on the vial.

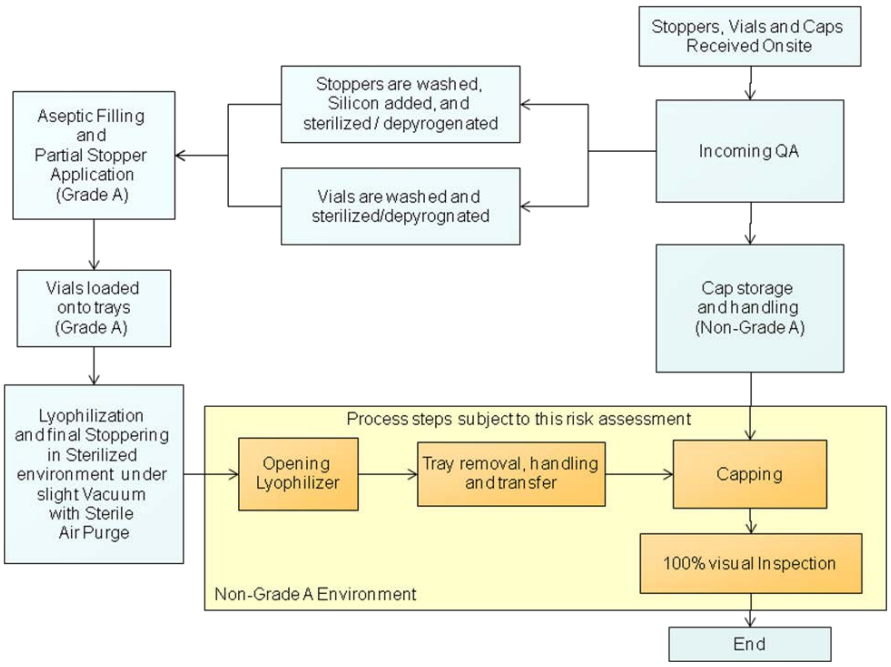

Figure 1

The example shows an FMEA type assessment, shown in **Table 7** below, at the step where the Vials are removed from the Lyophilizer, transferred to trays, which are then loaded into the capper.

REF #	Process Step	Unwanted Event	SEV	Cause / Process Failure	OCC	Current Controls	DET	RPR	Risk Accepted?	Recommended Actions	Ranking after actions			
											SEV	OCC	DET	RPR
2	***Remove trays from lyophilize, transfer trays to capper, and load trays into capper***	Lack of sterility assurance	H	*Stoppers are dislodged or missing*	M	*Procedural control for in-process visual verification of stopper presence, positioning (Qualification studies indicate this is a potential process failure)*	H	H	No (The cause happens and it is not easily detected)	*Add 100% mechanical stopper detection at capper in-feed (This would increase the likelihood of detection and therefore reduce the risk)*	H	M	L	M
2a										*Redesign handling system to eliminate cause (This modification would decrease the likelihood of the cause from occurring and therefore reduce the risk)*	H	L	H	M
2b										*Combine Actions from #2 and #2a*	H	L	L	L

Table 7

The first step identified ***Lack of sterility assurance*** as an unwanted event (i.e. a failure) and this is always given a high severity rating, so red.

The next step looks at possible causes of the failure, and it was agreed that this could happen if the stoppers were dislodged or missing. What is the probability of this happening (or the likelyhood of its occurrence)?

- If it almost always occurs it is Red
- If it almost never occurs it is Green
- Everything else is Yellow.

In this example it was believed that neither of the first 2 options are appropriate. So, it was deemed to be yellow as shown in the occurrence box in Table 7.

Moving across the FMEA assessment, the current controls to prevent the failure, and the likelihood of detection, were assessed. In this example, likelihood of detection, based on current visual check controls, was considered to be 'not likely': thus a rating of red was considered appropriate.

Actions to increase the possibility of detection were evaluated such as:

- Add 100% mechanical stopper detection at capper in-feed. This would increase the likelihood of detection and therefore reduce the risk. In this case, the detection rating moved to green, but the occurrence is not changed, and the severity is still high.
- Redesign handling system to eliminate cause. This modification would decrease the likelihood of the cause from occurring and therefore reduce the risk. In this case, the occurrence would reduce, thus the rating is now green, but the opportunity for detection is still low, thus it remains red.

However, if the two recommend actions are employed, both the detection and the occurrence become green, thus the overall risk (RPR) can become acceptable. This improves the process, and that is the objective!

The next case study looks at the next phase of how QRM can drive process improvement.

CASE STUDY 4: Applying a quantitative model for risk-based intervention control

This is a case study, which uses risk as a basis for evaluation of aseptic processing interventions, which introduces an Intervention Risk Assessment Model (IREM) which is published by DHI Publishing in a book chapter in 2013 (3). This example shows how a company could find measurable objective data on which to base the risk assessment.

The initial aseptic process simulation procedure stated that every intervention they carry out on-line, or on a set of lines, needs to be included in their media fill. (While the author does not necessarily agree with that approach, that was the procedure in place in the company at the time). Over the course of many years of manufacturing, they accumulated 50-60 interventions. As they had to put every one of those interventions

into every media fill, their media fills became intervention festers!

They decided they had to do something to fix this. What they did was attempt to rank the interventions in some way based on risk, and use this ranking to make a decision on whether to include them in the media fill, or not.

Initially they set up a team to devise an objective way to measure and rank the interventions. They came up with a 273-page SOP to do this! While the method had a lot of calculations - all of these were based on subjective opinion - it became apparent it was useless. They recognised they needed a different approach, so they set about developing a new model with specific criteria.

Model Criteria

The new model had to have the following 4 attributes:

1. Objective
2. Simple
3. Reproducible/robust
4. Logical.

The way they measured objectivity was in my opinion very interesting. It was that:

> *'No matter who used the model (i.e. anyone involved in aseptic operations) they would get the exact same results as anyone else using the model.'*

It had to be *simple*, as they wanted everybody to be able to use the model. They didn't want the model to be only usable by a select group of experts.

It had to be *robust* enough that it was applicable to all possible interventions.

Finally, it needed to be *logical*, as it would have to be presented to auditors and regulators, and its use defended.

Establishing the Model

The initial step in establishing the model was the creation of a diverse team with representatives from quality, manufacturing, validation, engineering, line mechanics, line operators, cleaning personnel, microbiologists, etc. The first task of the team was to ponder:

> *'If we can't measure the risk of the intervention, what can we measure?' Are there pieces, or something about the intervention, which we could measure?'*

In order to do this, the team employed what they called a KEY WORD approach, which led to a series of factors or criteria such as wording and numbers, which rang true to the team. These factors may not be universal, they may not be true for another plant, or for another operation process, or to another group. But to this team, who had to live with it and implement it: it made sense.

The team set the criteria and then avoided changing them. All the criteria or factors had to be measurable with the data readily available. In the model, the risk is determined by assessing a combination of all the factors, and as is typical with all models: a high risk is not acceptable.

The model process

Step 1: Brain storming session with informed Stakeholders

Determine Risk Factors: What factors contribute to risk of sterility failure as a result of an intervention?

The initial factors identified during the brainstorming session were quite numerous, and included such factors as:

- Closeness to the exposed product or product contact surfaces
- Difficulty in performing the intervention
- Frequency of the intervention
- Time it takes to perform the intervention
- Condition or exposure of the product or product contact surface during the intervention
- Control measures in place to prevent contamination
- Redundant control measures or subsequent processing which could reduce the effect of contamination
- Operator training required to perform the intervention
- Process failures or non-conformities linked to process failures.

As the factors identified have to be measurable and the data must be available, it must be simple. So, only a small number of factors should be evaluated.

Step 2: Consolidate the list into measurable risk elements

The 3 factors the team proposed were:

- Duration
- Complexity
- Proximity

Step 3: ***Set the metrics*** *(as shown in* ***Tables 8, 9*** *and* ***10*** *below)*

Duration

Risk Rating	Duration of intervention
High	*Greater than 10 minutes*
Medium	*Greater than 1 minute, but Less than 10 minutes*
Low	*Less than 1 minute*

Table 8

Complexity

Complexity	Number of Steps required to perform the intervention
High	*Greater than 5*
Medium	*2 to 5 steps*
Low	*1 step*

Table 9

Proximity

Risk	Proximity to exposed product contact surfaces* (Grade A area)
High	*Operator breaks first air during intervention with "body" and/or gloved hands*
Medium	*Operator breaks first air with sterilized tool or instrument (e.g. forceps)*
Low	*Intervention performed outside critical area*

Table 10

**It should be noted that later versions of the model changed the proximity criteria*

The team then evaluated all the 50 or 60 interventions with respect to the above criteria to set up metrics. For *Duration* they determined that 80% of the interventions had a duriation of between 1-10 minutes. By the metrics above, that is a yellow risk factor. Anything above that will be red, so is of more concern. Anything less will not be of concern.

For *Complexity* they determined that 80% of the interventions had 2-5 steps, so were a yellow risk factor. The 10% above were of more concern, and the 10% below that were not of as much concern.

Determining *Proximity* proved to be more challenging. The criteria they agreed upon were:

- The mid-level occurs when the intervention involved getting in the critical zone of breaking first air, with a sterilised entity (such as sterilised forceps, or an uncompromised, sterile glove)
- The high level occurs when the intervention involved breaking first air with an entity which was no longer in a sterile state (such as your sleeve, gown, or sanitised glove)
- The low level occurs, if first air is not broken at all.

Step 4: Run the Model

The fourth step the team carried out to run the model was to evaluate both *complexity* and *duration* using the risk assessment tool shown in **Table 11** below.

		Duration		
		Low	Medium	High
Complexity	High	*Risk Class 2*	*Risk Class 1*	*Risk Class 1*
	Medium	*Risk Class 3*	*Risk Class 2*	*Risk Class 1*
	Low	*Risk Class 3*	*Risk Class 3*	*Risk Class 2*

Table 11

From this evaluation, a Risk Class is determined, with Risk Class 1 (Red), Risk Class 2 (Yellow) and Risk Class 3 (Green).

These Risk Classes (which are artificial designations) are then considered in tandem with Proximity using the Risk Assessment tool shown in **Table 12** opposite, which gives us relative risk.

		Proximity		
		Low	Medium	High
Risk Class (Com & Dur)	Class 1	*Med Risk Priority - 2*	*High Risk Priority - 1*	*High Risk Priority - 1*
	Class 2	*Low Risk Priority - 3*	*Med Risk Priority - 2*	*High Risk Priority - 1*
	Class 3	*Low Risk Priority - 3*	*Low Risk Priority - 3*	*Med Risk Priority - 2*

Table 12

It is from this that the overall risk of the intervention is determined. It can be High priority 1, Medium priority 2, or Low priority 3.

To illustrate how the model operates, it is useful at this stage to look at examples of the model in operation when assessing intervention risks.

Intervention Example 1: Removing vial from conveyer

Removing a vial which has fallen or is jammed in the conveyor is a common intervention in the vial capping step being Risk Assessed, and is shown in **Image 1** below. It is a one-step operation of less than one minute's duration. It is carried out using a sterilised forceps which is inserted into the first air zone.

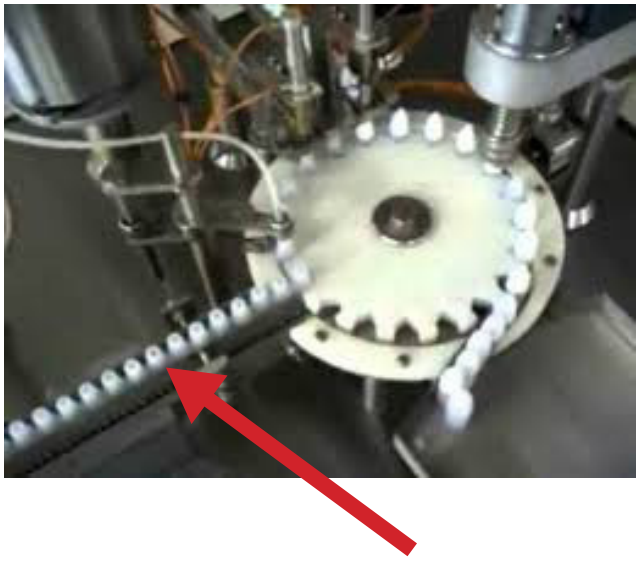

Image 1

Applying the risk model to evaluate complexity and duration, the Risk Class is determined to be Risk Class 3, which is low risk.

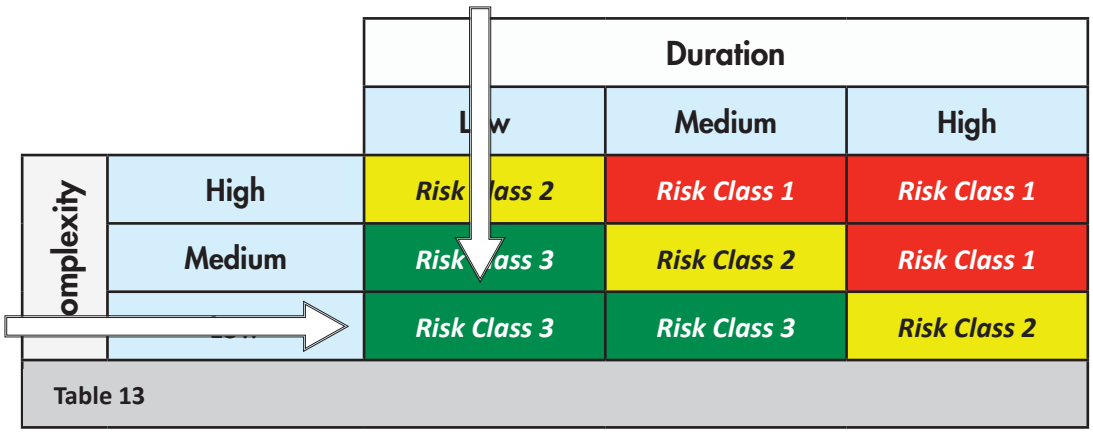

Table 13

Using Risk Class 3 in tandem with the criteria of Proximity, as shown in **Table 13** above, the overall risk is low, and given a risk priority of 3, as shown in **Table 14** below.

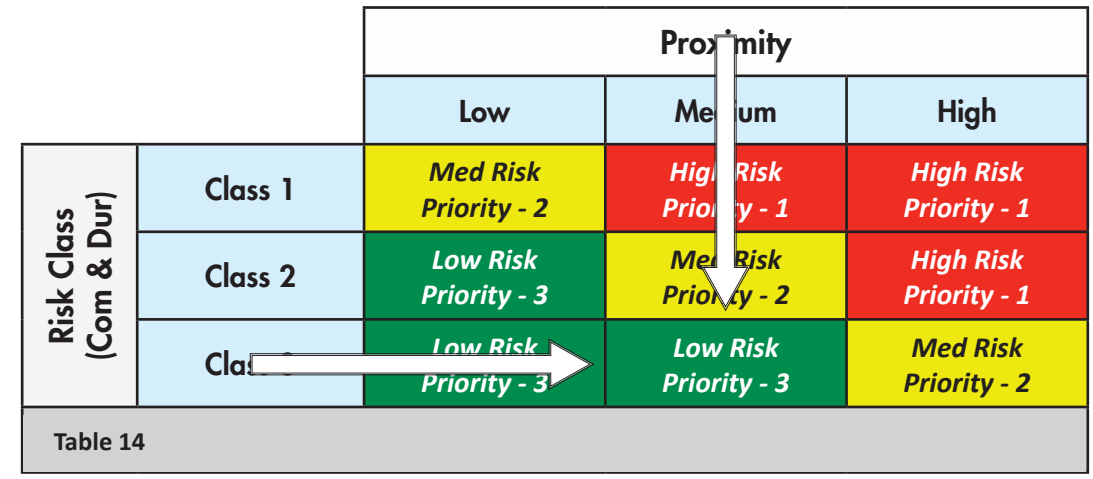

Table 14

Intervention Example 2: ***Removing a vial from stopper star wheel***

In this case the vial to be removed is in the stopper star wheel. Again, it is a one-step operation of less than one minute's duration. But this time the proximity has changed as the vial is deeper in the machine. In order to remove the vial, the arm has to enter critical space, as the gloved hand crosses track as forceps are used, thus entering first air.

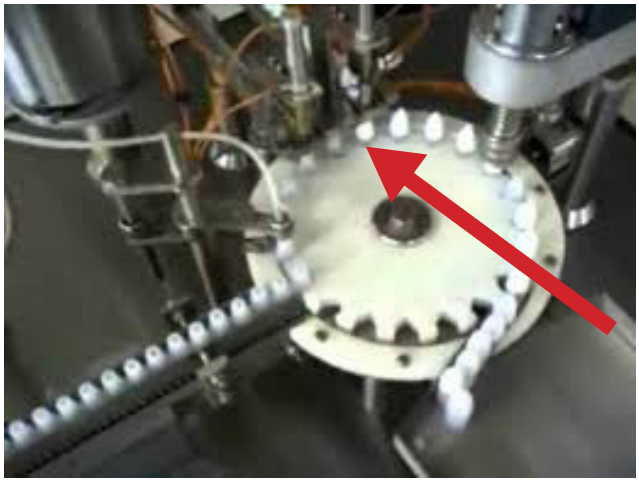

Image 2

Applying the risk model to evaluate complexity and duration, the Risk Class is determined to be Risk Class 3, which is low risk **Table 15**.

		Duration		
		L w	Medium	High
omplexity	High	Risk lass 2	Risk Class 1	Risk Class 1
	Medium	Risk ass 3	Risk Class 2	Risk Class 1
		Risk Class 3	Risk Class 3	Risk Class 2

Table 15

Using Risk Class 3 in tandem with the criteria of Proximity which is now medium as the gloved hand breaks, as shown in **Table 16** below, the overall risk Medium, and given a Risk Priority of 2.

		Proximity		
		Low	Medium	H h
Risk Class (Com & Dur)	Class 1	Med Risk Priority - 2	High Risk Priority - 1	Hig Risk Prio y - 1
	Class 2	Low Risk Priority - 3	Med Risk Priority - 2	Hig Risk Prio y - 1
	Class 3	Low Risk Priority - 3	Low Risk Priority - 3	Med Risk Priority - 2

Table 16

Step 5: Summarise, sort and evaluate relative risk of all interventions evaluated

The final step is to summarise, sort and evaluate the risk of all the interventions reviewd using the model. For illustrative purposes, we looked at 2 interventions, both assessing a Fallen Vial Intervention. These two would be summarised in a chart as in Table 17 below.

Intervention	Description	Duration	Complexity	Risk Class	Proximity	Risk
Removing vial from conveyor	In Grade A but outside first air, forceps used, one step, less than one minute in duration	Low	Low	3	Medium	Low
Removing vial from stopper star wheel	In Grade A, forceps used, but reach section of star wheel and conveyor across first air, one step, less than one minute in duration	Low	Low	3	High	Medium

Table 17

Comparing the two examples, which have similar interventions, you find that a higher level of risk is attributed to one. Prior to using the model, the risk would have been determined to be the same as it was figured it was the same operation, the same skill set, and thus the same risk.

What is interesting about this is: *The operators carry out this Risk Assessment* themselves as it is the operators who are determining the risk of their actions, (their interventions). They understand why one intervention has a higher risk than another. So, they are much more likely to comply with mitigating actions or procedures required (such as disinfecting the star wheel, removing bottles etc.) *when nobody is watching*.

To finish, we will look at 2 final examples which are slightly more complex and which focus on filler set-up. One is for a manually assembled process and the other for pre-assembled process, which is then Sterilised in Place (SIP).

Intervention Example 3: Manual set up of filler parts

In this intervention, to set up the filler, 8 fill needles are manually placed in a rack and hoses are attached to the pump as shown in **Image 3** opposite. The procedure takes over 10 minutes and involves over 5 steps. However, a non-sterile item does not disrupt the first air.

Image 3

Applying the risk model to evaluate complexity and duration, both are high as the task takes over 10 minutes and involved over 5 steps. Thus, the Risk Class is determined to be Risk Class 1, which is high risk, as shown in **Table 18**.

		Duration		
		Low	Medium	High
Complexity	High	*Risk Class 2*	*Risk Class 2*	*Risk Class 1*
	Medium	*Risk Class 3*	*Risk Class 2*	*Risk Class 1*
	Low	*Risk Class 3*	*Risk Class 3*	*Risk Class 2*

Table 18

Using Risk Class 1 in tandem with the criteria of Proximity which is now medium as the first air is not disturbed by a non-sterile item and as shown in **Table 19** below, the overall risk is High, and given a risk priority of 1.

		Proximity		
		Low	Medium	High
Risk Class (Com & Dur)	Class 1	*Med Risk Priority - 2*	*High Risk Priority - 1*	*High Risk Priority - 1*
	Class 2	*Low Risk Priority - 3*	*Med Risk Priority - 2*	*High Risk Priority - 1*
	Class 3	*Low Risk Priority - 3*	*Low Risk Priority - 3*	*Med Risk Priority - 2*

Table 19

However, we cannot accept a high risk, as that is the rule the company has set. So, the company explored using technology. In this case they introduced a Sterilisation in Place system (SIP). All the parts for filling are assembled and then the final assembled component is sterilised.

Intervention Example 4: Sterilisation in Place (SIP) setup

In this intervention, the fill needles are assembled in advance and sterilised off -line. The only critical intervention is the removal of covers after sterilisation. This task takes less than one minute. There are less than five steps, and a non-sterile item does not break first air.

Applying the risk model to this example, for complexity and duration, the Risk Class is determined to be Class 3, as shown in **Table 20**.

Complexity	Duration: Low	Duration: Medium	Duration: High
High	Risk Class 2	Risk Class 1	Risk Class 1
Medium	Risk Class 3	Risk Class 2	Risk Class 1
Low	Risk Class 3	Risk Class 3	Risk Class 2

Table 20

Using Risk Class 1 in tandem with the criteria of Proximity which is now medium as the first air is not disturbed by a non-sterile item. As shown in **Table 21** below, the overall risk is low, and given a Risk Priority of 3.

Risk Class (Com & Dur)	Proximity: Low	Proximity: Medium	Proximity: High
Class 1	Med Risk Priority - 2	High Risk Priority - 1	High Risk Priority - 1
Class 2	Low Risk Priority - 3	Med Risk Priority - 2	High Risk Priority - 1
Class 3	Low Risk Priority - 3	Low Risk Priority - 3	Med Risk Priority - 2

Table 21

Step 6: Summarise, sort and evaluation relative risk of all interventions evaluated

As discussed previously, the final step is to summarise, sort and evaluate the risk of all the interventions evaluated using the model. For illustrative purposes, we looked at the 2 interventions, both assessing a Filler Set Up interventions. These two would be summarised in a chart as follows in **Table 22**:

Intervention	Description	Duration	Complexity	Risk Class	Proximity	Risk
Manual set up	In Grade A fill needles placed in rack and then hoses are attached to pumps	**High**	**High**	**1**	**Medium**	**High**
SIP set up	In Grade A, SIP, intervention is the removal of the fill needle covers after sterilization	**Low**	**Low**	**3**	**Medium**	**Low**

Table 22

The above example demonstrates how employing technology to move a task from high risk to a low risk can result in process improvement. This gives the company evidence of how investing in the technology will reduce the risk. Indeed, by demonstrating the manual process to be a high-risk task, which the company determines to be unacceptable, they are obliged to reduce the risk and improve the process.

Concluding points

- The Risk Model does not have to be *complex*
- It should allow for *objective evaluation* of the Process with a view to *making improvements* rather than just identify risk
- Risk assessment provides *information* to make decisions, not make the decision
- The Criteria by which you judge the risk does not have to be perfect, but does have to be *meaningful*
- Understanding *why* is more effective than knowing *how*
- Set criteria before assessment, and no matter what, just *listen to the results*.

References

(1) PDA Technical Report 44,

(2) ICH Q9

(3) Intervention Risk Assessment Model (IREM) which is published by DHI Publishing in a book chapter in 2013. *Aseptic and Sterile Processing: Control, Compliance and Future Trends* – Hal Baseman and Mike Long, edited by Tim Sandle and Edward Tidwell

3.2 Drug/Device Combinations: Challenges faced when manufacturing combination products in a traditional secondary packaging facility

Martine Nolan, Head of Quality, Kiadis Pharma

For most of us seasoned pharmaceutical processionals we are very familiar with the manufacturing operations of API/bulk product manufacturing, or an aseptic manufacturing, under the well-known cGMP regulations. However, many of us will not be as familiar with working within the paradigm of medical device manufacturing. This can cause significant challenges for the traditional manufacturer, especially when manufacturing for multiple markets where the device regulations are not always aligned with medicinal product regulations.

Firstly, let me start by defining what medical devices and medical products are and the regulations that apply to them.

The US Section 201(h) of the Food, Drug and Cosmetic Act defines a medical device as:

> *"any healthcare product that does not achieve its principal intended purposes by chemical action or by being metabolised".*

Medical devices can be as simple as a tongue depressor or a thermometer or as complex as robotic surgical devices.

Regulations implementing FD&C Act – Title 21 Code of Federal Regulations (21CFR) Parts 800 – 1299

A Medicinal Product is addressed in Section 201(g) of the FD&C Act (21 USC 321(g)). The FDA regulations define the term drug, in part, by reference to its intended use, as

> *"articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease"*

and

> *"articles (other than food) intended to affect the structure or any function of the body of man or other animals."*

In the EU the regulations are somewhat similar: a medical device is defined as any instrument, apparatus, appliance, material, software, or other article […], alone or in combination, intended by the manufacturer to be used in humans for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury/handicap
- investigation, replacement, modification of the anatomy; control of conception
- and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.

*Council Directive 90/385/EEC and 93/42/EEC

Whereas a medicinal product is defined as a substance or combination of substances:

- having properties for treating or preventing disease in human beings,

or

- may be used in or administered to human beings with view to restore, correct, modify physiological function

or

- by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

*Directive 2001/83/EC

The FDA and EU regulations/ guidance diverge however when it comes to combination products as illustrated in the two figures below.

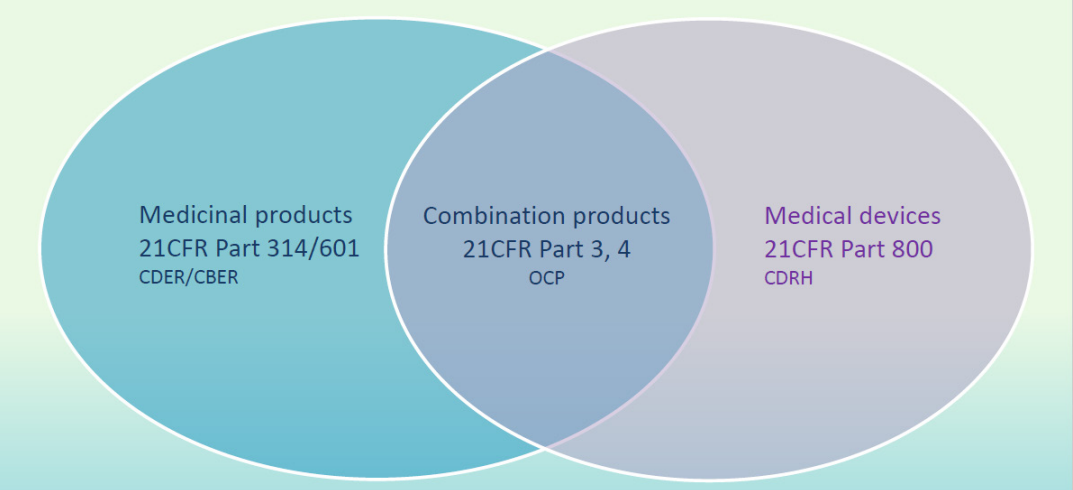

Figure 1 — FDA: "Combination products are defined as therapeutic and diagnostic products that combine drugs, devices, and/or biological products."

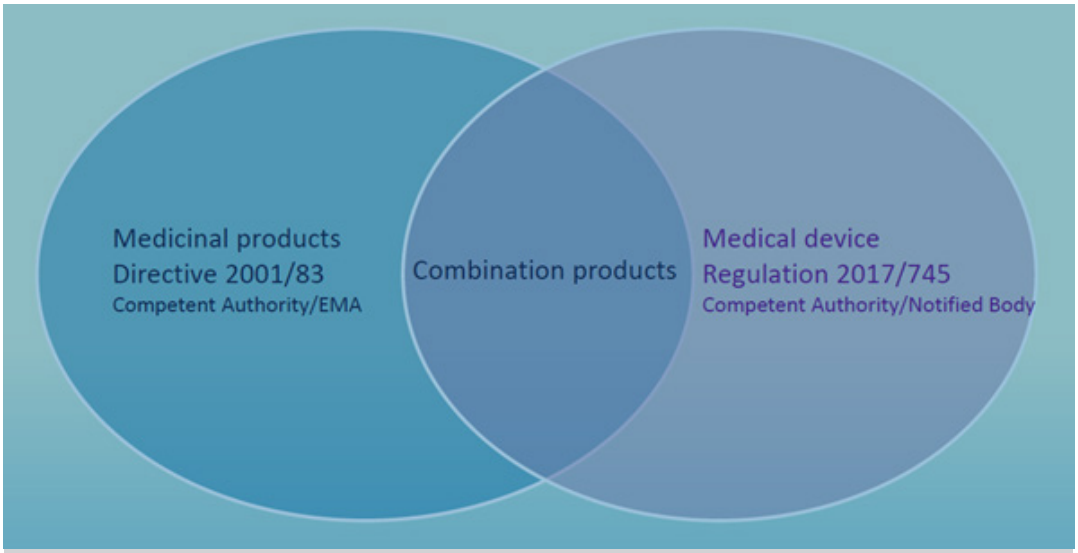

Figure 2 — EU: Combination products are not defined, but are mentioned in the scope of the medical device regulation

In the EU, there is no legal definition for a combination product where a medicinal product and a medical device are presented together either as an integral combination or presented separately for use together. The terminology in the context to this concept paper is restricted to medicinal products as defined by Directive 2001/83/EC.

For standard primary/secondary packaging operations the general approach is to follow the ICH Q10 Pharmaceutical Quality System. Introducing combination products however, requires several additional focus areas for the traditional manufacturer, especially those involved in fill-finish operations who many not previously have been performing secondary packaging activities. There is now a need to demonstrate compliance with both drug cGMPs and device Quality System regulations. This can best be achieved following a stream-lined approach where-by compliance with ONE complete set of cGMPs (drug or device) and the provisions specified in 21 CFR 4 from the other is demonstrated. This means supplementing the ICH Q10 based PQS with the following individual 21 CFR part 820 requirements:

- **820.20 — Management controls**
- **820.30 — Design controls**
- **820.50 — Purchasing controls**
- **820.10 — CAPA**
- *820.170 & 200 — Installation and Servicing*
  Generally only applicable to large, durable medical devices

820.20 Management Controls

Figure 3

For Management Controls there are two areas that need to be considered in particular when supplementing the PQS. These are responsibility and the management representation. In the case of management responsibility it is must be clearly demonstrated and usually at higher organisational level than required by 21 CFR 211

A Quality Management review process will most likely already by established where the performance of the PQS is regularly reviewed. To meet the requirements of 21 CFR 820.20 it is important to ensure that the right level of management attends review meetings and this is clearly documented. In large organizations where the overall Head of Quality is not physically located at the manufacturing facility, and does not attend these review meetings, it is required to have a letter of delegation from him/her to the representative on site- usually the Site Quality Head.

820.30 Design controls – including Risk Analysis

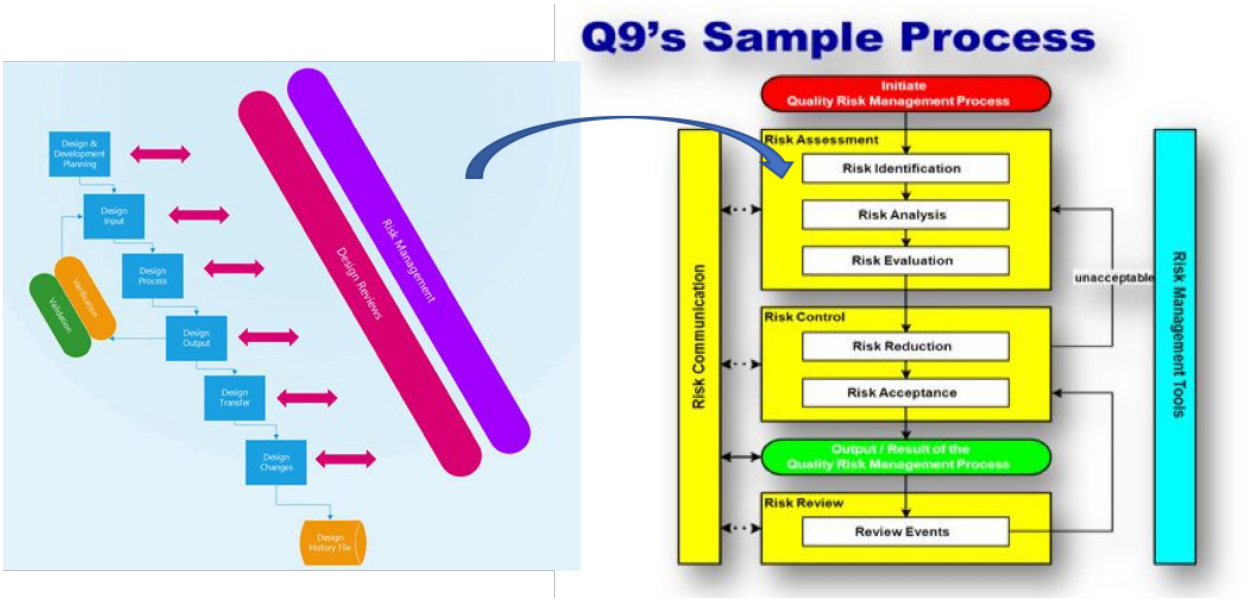

Figure 4

A significant challenge for most sites that take on the responsibility for the manufacturing of combination products is that the design is usually performed at an alternative location, for example, often at the company headquarters or by an alternative team e.g. a global device design team. Much of the detailed knowledge of the design of the device is held by these teams often with limited knowledge transferred to the site. As part of the tech transfer to the site it is crucial that the site fully understands the constituent parts' design specifications for each specific combination product. Having access to the key subject matter experts and a working knowledge of the additional design documentation required e.g. the Design History File is a must.

Quality Risk Management is a key part of the ICH Q10 PQS and having a robust Risk Management process should be one of the fundamental processes in place at a manufacturing site. The "Risk Analysis" referred to in 21 CFR 820.30 calls out specific steps including "risk identification/risk assessment/risk control" as described in the Risk Management documents ISO 14971 Standard for devices and ICH Q9 Guidance for drugs, as shown in **Figure 4** above.

820.50 Purchasing Controls

Management of suppliers and the controls put in place around the purchasing of device components requires robust use of Risk Management. One key challenge for most manufacturers is that manufacturing of devices is not their core business. They must rely heavily on the expertise of their suppliers and their knowledge of the mechanics of devices. It is crucial to establish and maintain procedures to ensure that all purchased or

otherwise received products and services meet specified requirements. Each supplier should be evaluated based on risks associated with the supplied product/service and the complexity of the specifications. As with all manufacturing accordance with cGMP it is necessary to properly maintain records for Contracts & Agreements and Product & Service requirements. Having a robust Change Management process is critical to ensure notification of changes to supply. Additional adequate document of the 21 CFR 211.84 testing requirements for Drug components and Container closure systems must be readily available.

820.100 CAPA

While the process of CAPA should be embedded at manufacturing sites it is usually focused on correcting and preventing deviations that occur related to the manufacturing or testing of an API, drug substance or drug product. When manufacturing involves a combination product the CAPAs can result from problems identified in constituent parts and/or the combination product as a whole. It is critical to consider implications of CAPAs to all constituent parts and combination product as a whole. It is also important to consider CAPAs broader implications e.g. on other materials from a supplier. For most of us, we also need to consider the implication of such CAPAs to more than one site, often a global manufacturing network may be impacted and it is important to consider the global impact when implementing any process, product or device changes.

The complexity of investigations and CAPAs significantly increases with combination products and it is often the case that root cause of a deviation lies outside the direct scope of a manufacturing facility. It is then that the importance of robust purchasing controls becomes evident, as shown in **Table 1** below.

Scope of investigation	Root Causes	CAPA
High Activation Force Results during in process testing	Root Cause is assembly equipment causing damage to internal parts of rear subassembly	1. Equipment modifications implemented 2. Spec limit revision drug
Device not activating	Root Cause is combination of materials (after mold maintenance by manufacturer) and vibration/ shock during assembly process	1. Equipment modifications implemented 2. Change of Device Design
Injection Time OOS, covering syringe barrel, stopper, fill/formulation, device, packaging, method	Root cause is combination of poor syringe barrel siliconization, with high spring force variability in rear subassembly that was still within specification	1. Manual screening of rear sub assembly batches for spring force variability as a short-term measure 2. Optimised control strategy at manufacturer including characterisation of siliconization profile and stopper characteristics
Injection Time OOS, covering syringe barrel, stopper, fill/formulation, device, packaging, method	Root cause is combination of internal friction within injector, syringe barrel siliconization, and stopper geometry	Alignment opportunities with other sites (sampling handling, in-process testing device cleaning method/ frequency)

Table 1

In parallel to the additional manufacturing complexity of combination products, the complexity of regulatory inspections is also increased. A site that manufactures combination products now has the possibility to be inspected by both product and device inspectors. This can prove to be very challenging when hosting simultaneous inspections. If the device expertise is located at an alternative location then it is important that the device knowledge be transferred completely to site personal or the relevant subject matter experts be present at the site to support the inspection in real-time. The focus areas of the inspectors may overlap so it is important to manage the inspection support resources to ensure their availability for both device and product inspectors.

In summary, when manufacturing combination products there is a need to manage ever increasing complexity across the whole supply chain. There are many aspects regarding Product Specific Requirements that may need to be shared across several facilities, in addition to Facility Specific Requirements which relate to the product testing within a specific facility. The complexity of devices requires enhanced supply controls. The Quality Management System needs to incorporate the specific device requirements. Lastly regulatory inspections are becoming more complex as the scope expands to include adherence to device regulations.

Part 4: Technology Innovation Matters

4.1 Industry 4.0 in pharma: demystifying the techno-jargon and focusing on the 'Why?'.

Exploring the evolving digital landscape supporting Quality Risk Management and Knowledge Management in product realisation

Barry Heavy, Director Life Science Practice, Accenture

1. An industry coping with increasing complexity

The global pharmaceutical industry faces a growing complexity challenge as a greater proportion of the industry portfolio migrates to more complex drugs and drug-device combinations. The growth in complexity can be quite simply illustrated by the fact that the best-selling drug in 2007 – Lipitor - contained 33 carbon atoms[1] and was formulated in simple tablet form, whereas the best-selling drug today – Humira- containing 6624 carbon atoms[2], is formulated in a sterile liquid form and is typically delivered by a complex autoinjector designed to help patients with arthritis to easily self-administer. In addition to the fact that a large proportion of new drugs are in the higher complexity category, these new drugs are also emerging from research and development at a faster pace, with cancer research being an area where new drugs are regularly fast-tracked to approval based on their impressive results in trials[3] . This means that companies have less time to develop manufacturing processes for drugs that are increasingly complex.

Drugs are also increasingly targeted at smaller patient populations and are highly potent, so do not need to be made in large quantities. This can result in many facilities becoming multi-product production sites, with a variety of small-batch-size processes, diverse recipes and technology platforms, and flexible equipment trains.

An extreme example that encapsulates all of the above is the emergence of cell therapy such as CAR-T cells. These therapies are extremely complex in that they are made with living cells which have been genetically modified. They have emerged extremely rapidly in recent years from academic research in the University of Pennsylvania in 2011[4] to FDA approval in 2017[5]. Furthermore, they are the ultimate example of low volume, high mix production, with each batch being made for an individual patient. This creates enormous complexity for manufacturing, quality control and supply chain.

With the growing importance of biologic drugs comes the growing importance of the parenteral route of

1 https://en.wikipedia.org/wiki/Atorvastatin
2 https://en.wikipedia.org/wiki/Adalimumab
3 https://www.bmj.com/content/351/bmj.h4633
4 https://www.nejm.org/doi/full/10.1056/NEJMoa1103849
5 https://www.novartis.com/news/media-releases/novartis-receives-first-ever-fda-approval-car-t-cell-therapy-kymriahtm-ctl019

administration to avoid digestion of these complex biologic drugs in the GI tract. This in turn creates an increased focus on the drug-device combination to make it easier to administer the drug parenterally. Savings can be made in healthcare costs by moving administration to the patient's home rather than in the infusion centre by utilising advances in formulation and easy-to-use devices like pen injectors, autoinjectors and patch-pumps. When a device is being utilised it also opens up possibilities to move to *smart devices* that contain microelectronics and communications systems to monitor the use and condition of the device, and to provide support to the patient or care provider through connectivity to apps. Such technology and app-based services *wrapped around* the drug can differentiate a treatment in the marketplace by providing a better experience to the patient/carer but it, in turn, brings additional complexity to the supply chain. Now the company is responsible for both complex drugs and for complex devices which are often based on technology such as embedded software, sensors etc. with which they may have limited experience.

Finally, the outsourcing of aspects of manufacturing and quality testing remains important in the industry but also brings complexity. There exists a significant amount of spare capacity in the industry in traditional API and solid oral dose production, with few new sites being built in the US and Europe in the last decade, and with many existing sites in Europe and US being acquired by contract manufacturing organisations (CMO). This has created a *buyers' market* for Pharma companies in accessing CMO capacity for API and solid oral dose but companies must navigate carefully in choosing the correct CMO partner in this space as the CMOs active in this area are under enormous competitive pressure, which in turn can create risk. In contrast, in the biologics manufacturing space, there are only a few established contract manufacturers with a track record and capacity for biologics production. This creates a *sellers' market* where pharma clients have less choice and face significant costs in engaging CMOs.

This increased complexity has played a significant role in driving Pharma 4.0, as illustrated in **Figure 1** below.

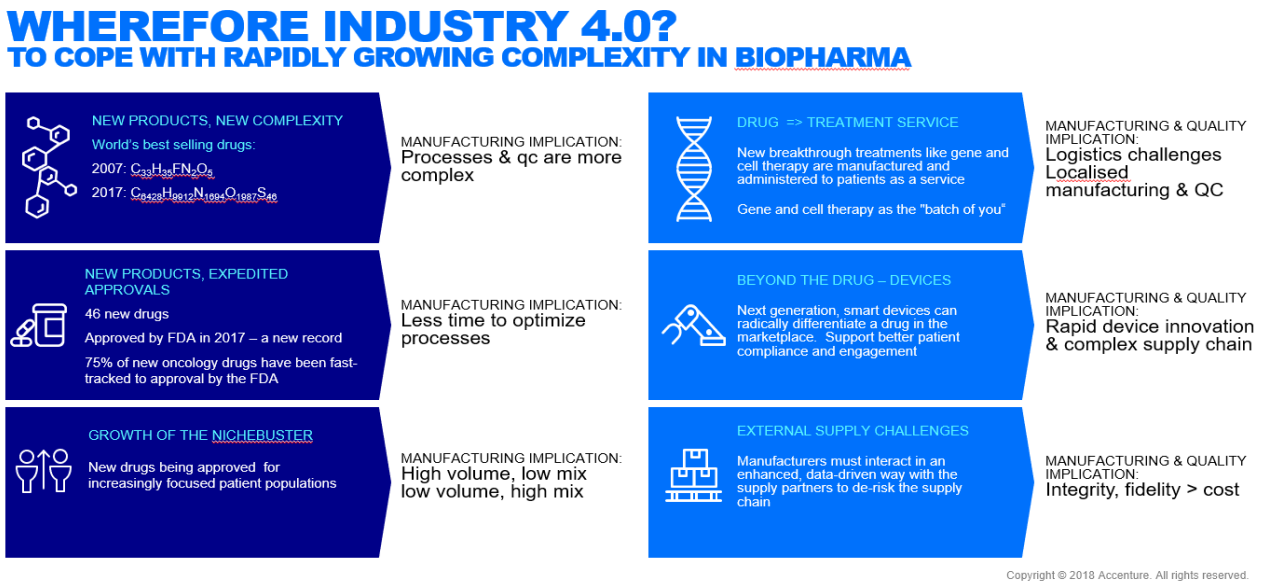

Figure 1

2. Why Go Digital and embrace industry 4.0?

The recently retired FDA commissioner Scott Gottlieb issued a statement about novel treatments like cell and gene therapy saying that "some of the more challenging questions… relate to product manufacturing and quality..."[6]. The increasing complexity faced by the industry as outlined above is why old, analogue methods for managing data, risk and knowledge in manufacturing are becoming untenable. A digital architecture can help to ensure that companies and their diverse manufacturing sites are able to cope with moving from a high volume, low mix production, to a low volume, high mix paradigm.

Pharma companies have already embraced digital in other disciplines such as R&D and commercial realms, but manufacturing and quality have been somewhat slower to adopt digital. Companies have been embracing digitalisation for decades as they dealt with more complex data in R&D. The term *Bioinformatics* was already used widely in drug discovery and clinical research circles in the 1990s as companies started to grapple with the complexity of data from genomics, proteomics and transcriptomics and medical imaging research. Today we see drug discovery arms of pharma companies on the cutting edge of digital with Biogen investing in quantum computing to help give them a competitive edge in drug discovery [7]. By comparison, manufacturing is underinvested in digitalisation despite being downstream of the fruits of the digitalisation trend in R&D: new drugs are emerging faster from R&D in part because of R&D's ability to utilise richer datasets and make faster decisions about more complex treatment modalities for more precisely defined disease states. Manufacturing runs the risk of becoming a bottleneck for innovation if it struggles to cope with this new complexity and speed due to underinvestment in digital.

3. Is Industry 4.0 just a marketing buzzword? Isn't the Pharma industry already doing this?

Industry 4.0 is a term that has come strongly into vogue in recent years. The concept emerged from a German government strategy paper in 2010 called "High Tech Strategy 2020"[8] which led German industry groups to establish "Plattform industrie 4.0" in 2013[9]. This group defined industry 4.0 quite succinctly as "intelligent networking of machines and processes for industry with the help of information and communication technology". The concept of a 4th industrial revolution was based on the concept that Industry 1.0 was based on mechanisation through steam power, Industry 2.0 utilised electrification, Industry 3.0 saw the introduction of computer control systems and robotics into manufacturing. But the vision for Industry 4.0 would see a genuine new "step-change", a move from "islands of automation" in the factory to fully connected systems – effectively "joining the dots" in the data landscape. It is possible to use lots of additional buzzwords to describe this such as *internet of things*, *cyberphysical interfaces* and *internet of systems*. But irrespective of

6 https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm613026.htm
7 https://pharmaphorum.com/news/biogen-quantum-drug-development/
8 https://ec.europa.eu/digital-single-market/en/blog/implementation-industry-40-strategy-german-plattform-industrie-40
9 https://www.plattform-i40.de/PI40/Navigation/EN/Home/home.html

how one collects and connects data, the basic concept is that as data flows across the system and the network of sites, the potential for using data analytics or machine learning to drive optimisation and risk mitigation would increase.

Operational technology such as automation and distributed control systems have already been well established in the pharma manufacturing space, and there was an enormous push to utilise process analytical technology (PAT) in the last decade to gather more data on what was happening in reactor vessels in real-time. But despite this investment, there is an argument that the pharma industry is firmly in an industry 3.0 era and has not fully joined the dots between different data silos to truly unlock the value of the data they gather and convert it into insights and knowledge. Industry 3.0 may have served the pharma industry well for the past decades but there is an argument that it will be insufficient to help companies deal effectively with the complexity challenge outlined in the previous section.

So, whether one embraces the Industry 4.0 terminology or not, the concept of connecting the dots between data sources is compelling when faced with increased complexity. Some of the issues with the current state of play in the pharma industry include the following:

- Automation systems in plants are often run as *islands* and are not connected to each other and paper still dominates in many plants
- IT systems like MES can be used to connect up the islands of automation but are often only partially deployed in a site (e.g. may only support weigh and dispense, rather than a full Electronic batch record) or only partially across a network (some sites electronic, different sites using different systems, other sites still on paper).
- Related IT systems which should ideally work in concert to support insight generation are often poorly connected. For example, systems covering manufacturing data (MES, historian) are often poorly connected to systems covering quality (QMS) and QC (LIMS, CDS). This siloed nature of IT systems could be in part reflecting the siloed nature of teams in manufacturing, and quality/QC in many sites.
- Data and insights gathering systems used in process development (lab notebooks: analogue or electronic) and manufacturing (MES, LIMS) are often poorly connected, limiting the ability to share insights and knowledge between the R&D and manufacturing/quality teams over time.
- Data from different sites and systems may the pumped into a data lake, but companies may not be investing sufficiently in the *engineering* of the data to retain key elements of the data *context* – this may hinder the ability to align key datasets and to surface insights quickly.
- Manufacturing and quality teams may struggle to make a sufficiently compelling business case for investing in digitalisation when competing for limited resources with colleagues in R&D or commercial. The argument that "data science will help discover better drugs or drive higher sales" may appear (on the surface) to be more compelling than "data science may lower risk in manufacturing & quality". This dynamic around investing to mitigate risk can change when the company or industry observes a significant risk being realised (such as recent challenges observed in some sterile manufacturing sites) but it is incumbent on the stakeholders to make a more compelling case to invest "ahead of the curve".

- The industry continues to need humans in the loop to run production. As batch sizes get smaller, the mix of products greater and the emergence of new products coming through the pipeline quicker, companies are moving to so-called *factory-of-the-future* technology such as single use systems. In this type of factory-of-the-future the human is still as important as ever: there are limitations to the use of highly customised, and hence sometimes inflexible, automation in a flexible factory. Operators working manually with single use systems and mobile skids provide more flexibility and agility. Humans working in the factory-of-the-future or a QC lab-of-the-future now regularly encounter IT systems and human-machine interfaces that are significantly less advanced and less agile than the technology they use in their everyday lives.

Best-of-breed MES and LIMS systems can help connect up different islands of automation and lab instrumentation and link this to core enterprise-wide IT systems like ERP. These tools can also help *augment the worker* who interacts with these systems. Batch records can be compiled electronically rather than on paper, enabling rapid review-by-exception and the worker is guided through a step-by-step process for batch execution, minimising the potential for error. Furthermore, novel user interfaces such as mobile interfaces and assisted or augmented reality and voice-interaction with the MES & LIMS system are now being trialled by companies. **Figure 2** explores some of the key drivers for the development of robust Knowledge Management systems.

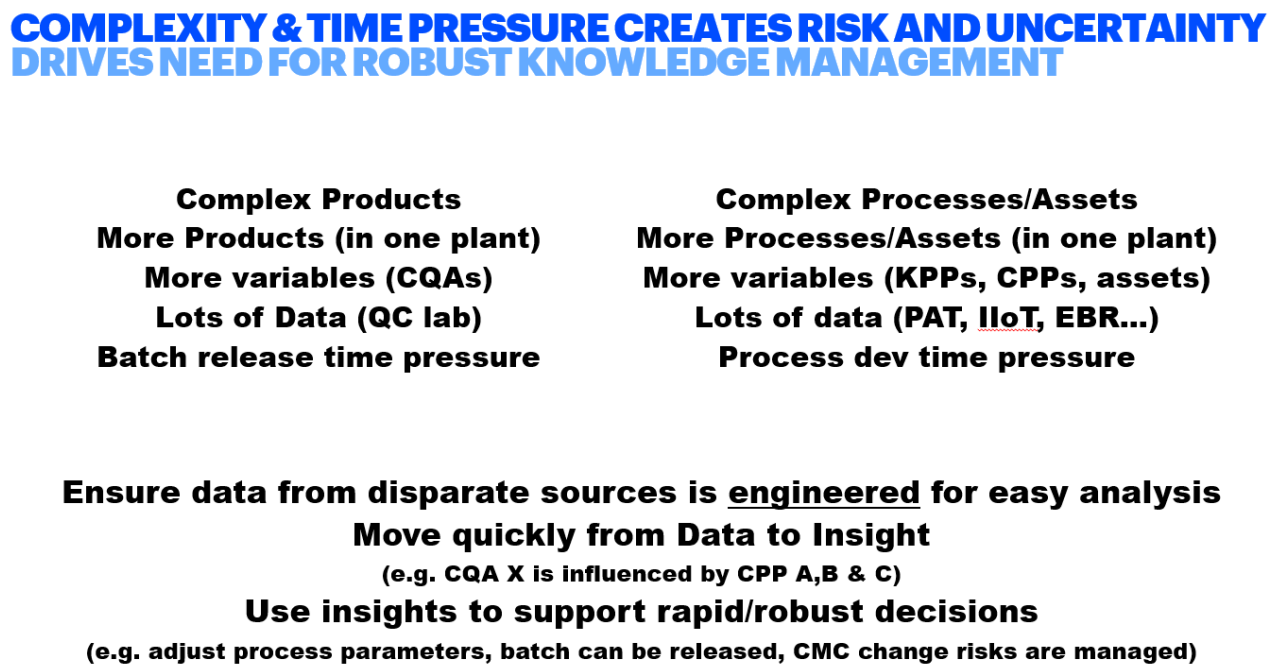

Figure 2

4. Connecting the dots between IT systems and unleashing Data Analytics

MES is used to create an electronic batch record of all the steps performed in the manufacturing process. Along with the historian system it can gather data on critical process parameters (CPPs). Lab information management systems (LIMS) are used to record the laboratory data on raw materials used, on process samples and on final product produced. It can provide data on critical process parameters (CPAs). QMS systems support and record the application of quality principles systematically to various business processes. Ultimately these manufacturing and QA/QC data sets must be combined for audit, but these data can also be combined and analysed to create value: How are CQAs influenced by CPPs? What deviations are arising repeatedly and how might this be addressed?

Advanced analytics between these data sets can surface insights, correlations and trends that may be important for manufacturers to fully understand how their process is performing over time, to identify root cause for problems, to improve productivity/ robustness in a data-driven way, and to mitigate risk of batch failure or a delay in batch release. For products which can be life-saving for patients and have multi-billion dollar annual sales, these data-driven insights are vital.

Accenture has been acquiring boutique companies who specialise in some of these systems because we see the importance of digitalisation in these areas and the value of connecting the dots between these systems. In 2017 Accenture acquired the US company LabAnswer who specialise in LIMS and other IT systems in Quality such as Quality management systems (QMS), Chromatography Data Systems (CDS), Electronic Lab Notebooks (ELN) etc. In March 2019 Accenture acquired the Irish company Enterprise Systems Partner (ESP) who share many similarities with LabAnswer, but who specialised in MES system integration in pharma. The MES market was valued at $7.6bn in 2015 and is estimated to be reach $18.2 billion by 2022 [10]. Life sciences is a key subsector within the MES market: the high level of regulatory focus on production of high quality and consistent medicines means that precision and robust record keeping in manufacturing is vitally important. ESP also diversified into supporting pharma companies in implementing serialisation, i.e. the ability to track and trace all product manufactured, in order to lower the risk of counterfeit medicines entering the marketplace. Accenture sees huge synergies between LabAnswer and ESP and with our capability in Accenture Digital, where we have deep expertise in data engineering and data science, as well as technology such as machine vision, AR/VR and artificial intelligence which can be layered on top of core manufacturing and quality IT systems, see **Figure 3** opposite.

[10] http://www.rnrmarketresearch.com/manufacturing-execution-system-mes-market-global-forecast-and-analysis-2011-2016-by-applications-process-manufacturing-industries-chemicals-oil-and-gas-pulp-and-paper-food-and-beverages-wat-market-report.html

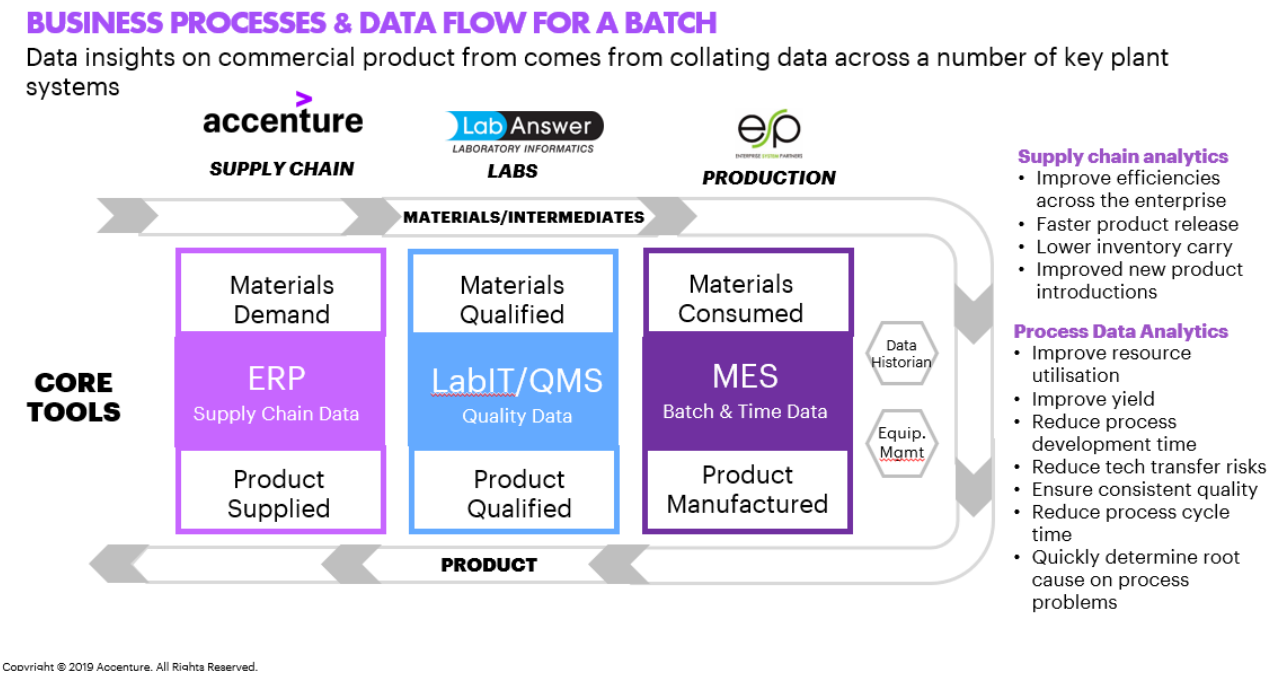

Figure 3

5. Where to next? Digitally-enabled collaboration between manufacturing and R&D?

As research accelerates in life sciences, [11] Accenture sees a need for pharma companies to break down the silos between their R&D and manufacturing/QC teams. There is a need for more integrated systems to support collaboration across different teams, different geographies and across the lifecycle of a product. A connected architecture of data gathering systems is the digital thread that supports knowledge development, management and sharing between R&D, manufacturing, quality and supply chain, between biochemists, chemical engineers and data scientists, and between internal and external workforces.

Other R&D intensive industries such as the aerospace and automotive industry have well-established tools for supporting this kind of collaboration and knowledge sharing across teams, geographies and time. Product Lifecycle Management (PLM) software is commonly used as an enterprise level tool to support this imperative. PLM tools have been commonly deployed in the discrete manufacturing industry where the product is designed and the computer aided design (CAD) file is central. With these tools the design assumptions and early testing data can be handed off to manufacturing and manufacturing teams can provide data-driven, evidence-based input on challenges they foresee or have faced with production/QC of this product or similar products. Thereby the teams can work cohesively to address problems/risks quickly, or even before they arise.

[11] https://www.bmj.com/content/351/bmj.h4633

In pharma the drug is discovered, not designed. But the process is designed, the recipe is optimised and the process can *evolve over time*. The phrase the "process is the product" became popular in the industry especially as more biologics emerged and industry stakeholders including innovator companies, generic companies, regulators and academia, debated the risks associated with biosimilar versions of off-patent biologics. The issue at stake was that a slightly different process used by the biosimilar manufacturer might result in some fundamental changes to the product, such as post-translational modifications which might alter the efficacy and/or safety of the biosimilar vis-à-vis the reference drug. This risk is higher in mammalian-cell produced biosimilars because of their increased complexity and post translational modifications.

However, this same risk of a *change to the product* also faces the innovator companies every time they make a *change to the process*, such as during scale up, tech transfer or in attempts to intensify the process (e.g. boost grams per litre), a desire to remove undesirable raw materials (e.g. eliminate dependence on serum) or a desire to switch to a new technology (e.g. embrace single use systems or improved chromatography resins).

The very long clinical trial process, averaging 10 years, that was the norm in the industry meant that process development team had longer to optimise and understand the process before making their CMC filing. However, now, with compressed timeframes, and with new modalities like bispecific antibodies, antibody drug conjugates and cell & gene therapy, the time to design and test the process is shorter. This will likely often lead to companies having to settle on a suboptimal process at launch with significant need for further optimisation/redesign over time. The need for collaboration between manufacturing, quality and process development teams will become more important.

For these reasons I believe it is vital for manufacturing and quality leadership in pharma to start reassessing their operating model and to explore new ways to foster collaboration and knowledge sharing with colleagues in R&D. New tools that can enable this collaboration and lower the risks associated with analogue knowledge transfer will be hugely valuable, but only if they are embraced by the key stakeholders, and designed specifically to solve their particular problems.

Figure 4 illustrates how the digital thread should be applied across the product lifecycle and **Figure 5** shows the importance of appropriate Knowledge Management for data gathered.

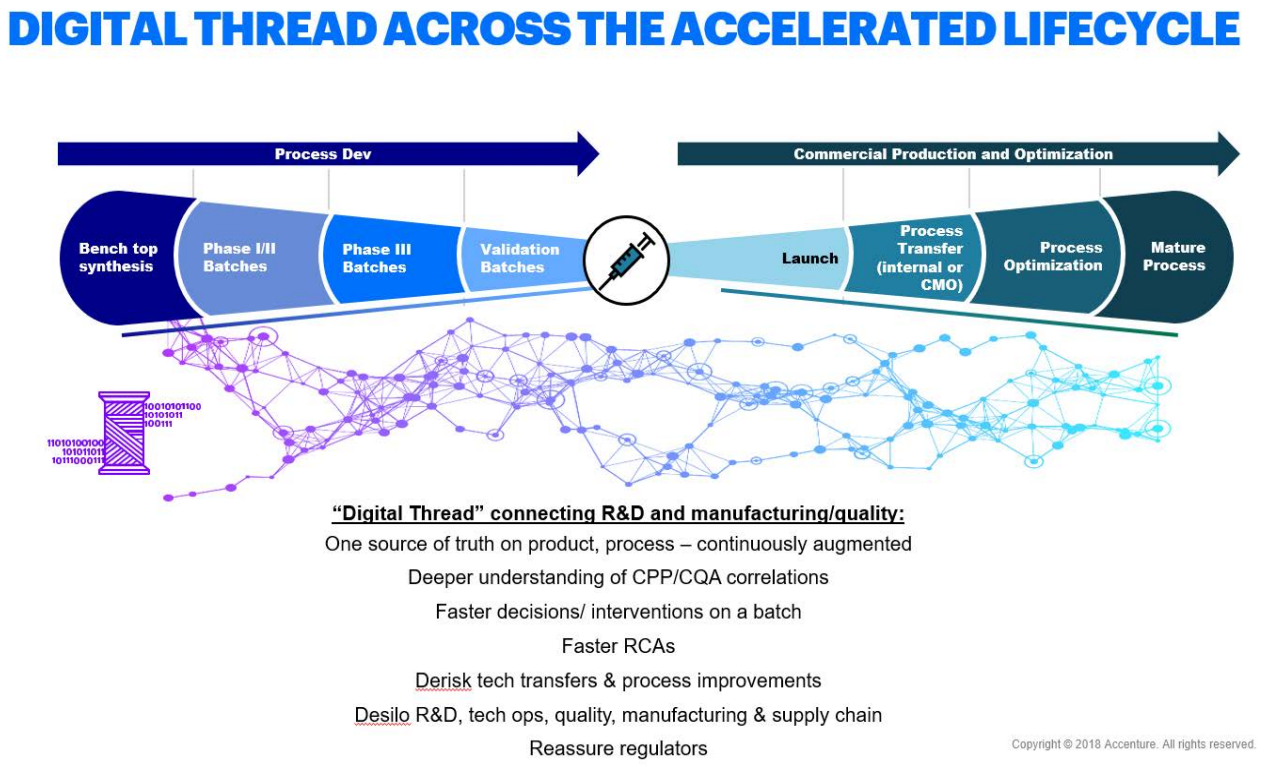

Figure 4

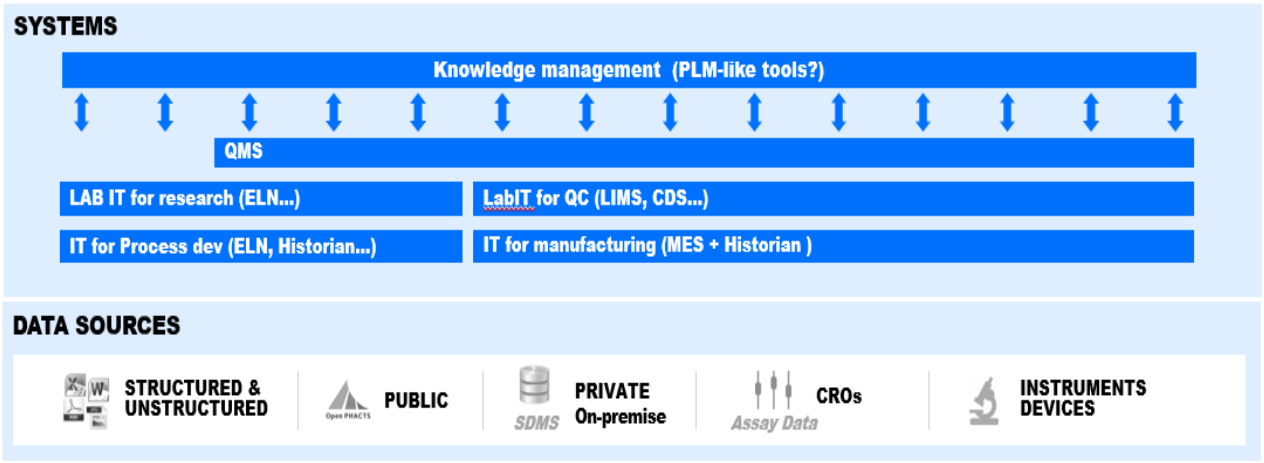

Figure 5

6. Summary

This article was written to support a discussion on Quality Risk Management and Knowledge Management in Product Realisation. I have tried to outline that the industry is facing a complexity challenge with increased potential for variability and, in-turn, increased potential for risk around inconsistent quality.

Accenture's consultancy work in the pharma industry is heavily focused on how the deployment of technology, combined with business process change, can help companies to deal with the challenges they face. Hence, I

have tried to illustrate how other parts of the pharma industry, such as R&D, have embraced digital tools to capture, curate and analyse data on complex topics, manage knowledge across silos (discovery and clinical) and geographies and mitigate risk in drug discovery and clinical development.

I have discussed my views on how the manufacturing and quality groups have some gaps in their adoption of digital tools compared to their peers in R&D. I have tried to outline how best-of-breed IT systems can *augment the worker* and help lower the risk of human error in manufacturing.

Most importantly I have discussed how connecting the dots between IT systems and data silos, and utilising analytics, can help to surface important insights that will reduce risk and contribute to knowledge development, curation and sharing.

Finally, I have discussed how other R&D-intensive industries have used IT tools to support collaboration between teams in R&D, manufacturing and quality, and made a case for the pharma industry to start to explore utilisation of these tools combined with organisational change to break down the internal silos and to address the challenges and opportunities ahead.

The pace of change in understanding disease and in developing new drugs and new therapeutic modalities has never been faster. Process development, manufacturing and quality are increasingly on the critical path for bringing these new treatments to patients safely and cost effectively. In parallel the global manufacturing industry is in the midst of the 4th industrial revolution, with high tech industries like aerospace, automotive and microelectronics leading the way. The interface of these two megatrends is an exciting place to be.

4.2 The Role of Smart Manufacturing in enabling QRM & KM to realise safer and more affordable products for patients in the 21st Century

Luke Kiernan, Technical Services Director, Innopharma Labs

1. Introduction

For centuries all goods were manufactured by hand in cottage industries or with the help of work animals in the fields. By the beginning of the 19th century though, manufacturing began to change dramatically with the first industrial revolution or Industry 1.0. Operations have rapidly evolved through further industrial revolutions 2.0 and 3.0 to the current revolution or Industry 4.0. as illustrated in **Figure 1** below.

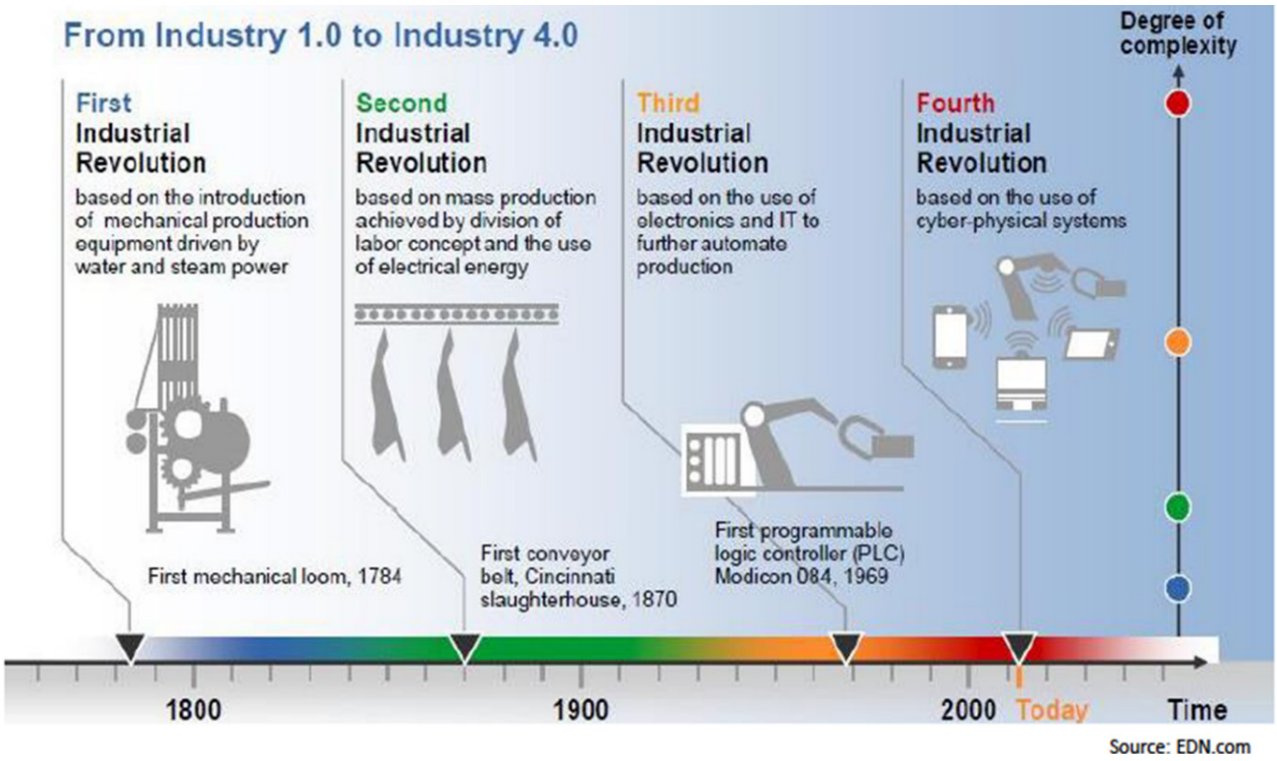

Figure 1: Industry 1.0 to Industry 4.0

Industry 1.0

From the invention of the first mechanical loom in 1784 and into the 1800s water-powered and steam-powered machines were developed to aid workers. As production capabilities increased, business also grew from individual cottage owners taking care of their own needs and those in their immediate locality to organisations with owners, managers and employees serving customers.

Industry 2.0

By the end of the 1800s electricity became the primary source of power. It was easier to use than water and steam, and it enabled businesses to concentrate power sources to individual machines. This made the use of assembly lines possible. The first electric assembly line was built in 1870. Assembly lines increased the efficiency and effectiveness of manufacturing facilities. Mass production of goods using assembly lines became commonplace. Industry further evolved with the concept of just-in-time and lean manufacturing principles, which further refined the way in which manufacturing companies could improve their quality and output.

Industry 3.0

In the last few decades of the 20th century, the invention of electronics and information technologies made it possible to further automate individual machines and thus to automate manufacturing processes. Technologies such as Ethernet connectivity, sensors, embedded intelligence, software solutions such as MES (manufacturing execution systems) and SCADA (supervisory control and data acquisition), and even data analytics, have all evolved during the third industrial revolution. Integrated systems, such as material requirements planning, were superseded by enterprise resources planning tools that enabled humans to plan, schedule and track product flows through the factory.

Industry 4.0

In the 21st century Industry 4.0 connects the industrial internet of things (IIOT) with manufacturing techniques to enable systems to share information, analyse it and use it to guide intelligent actions. It also incorporates cutting-edge technologies including additive manufacturing, robotics, artificial intelligence and other cognitive technologies, advanced materials, and augmented reality, according to the article 'Industry 4.0 and Manufacturing Ecosystems' by Deloitte University Press.

The Boston Consulting group has taken the concept further by identifying nine different pillars on which the foundation of Industry 4.0 is built, as illustrated in **Figure 2** opposite. Advanced digital technology is already used in manufacturing, but with Industry 4.0, it will transform production. It will lead to greater efficiencies and change traditional production relationships among suppliers, producers, and customers, as well as between human and machine.

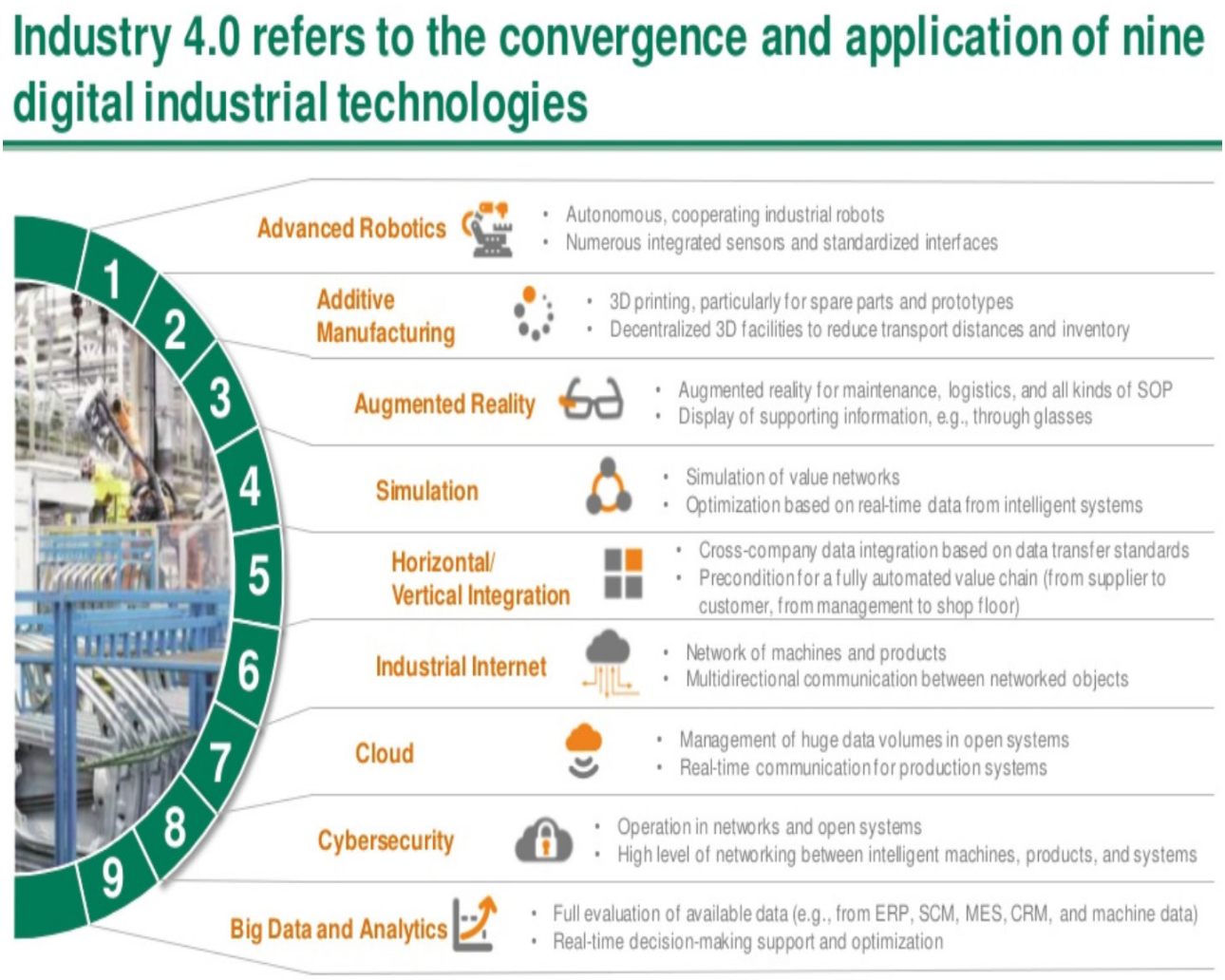

Figure 2: Industry 4.0, nine pillars

The development of new technology has been a primary driver of the movement to Industry 4.0. Some of the programmes first developed during the later stages of the 20th century, such as manufacturing execution systems, shop floor control and product life cycle management, were far-sighted concepts that lacked the technology needed to make their complete implementation possible. Now, Industry 4.0 can help these programmes reach their full potential.

The Evolution from 3.0 to 4.0

The transition from Industry 3.0 to 4.0 has been more of an evolution than a revolution with incremental increases in machines capability, complexity and control being achieved over time as again illustrated in **Figure 3**. The journey has taken industry from basic SCADA controlled machines, to greater use of the data generated, to ultimately turning the data into knowledge and subsequent control. New and better sensors have been developed, facilitating the journey.

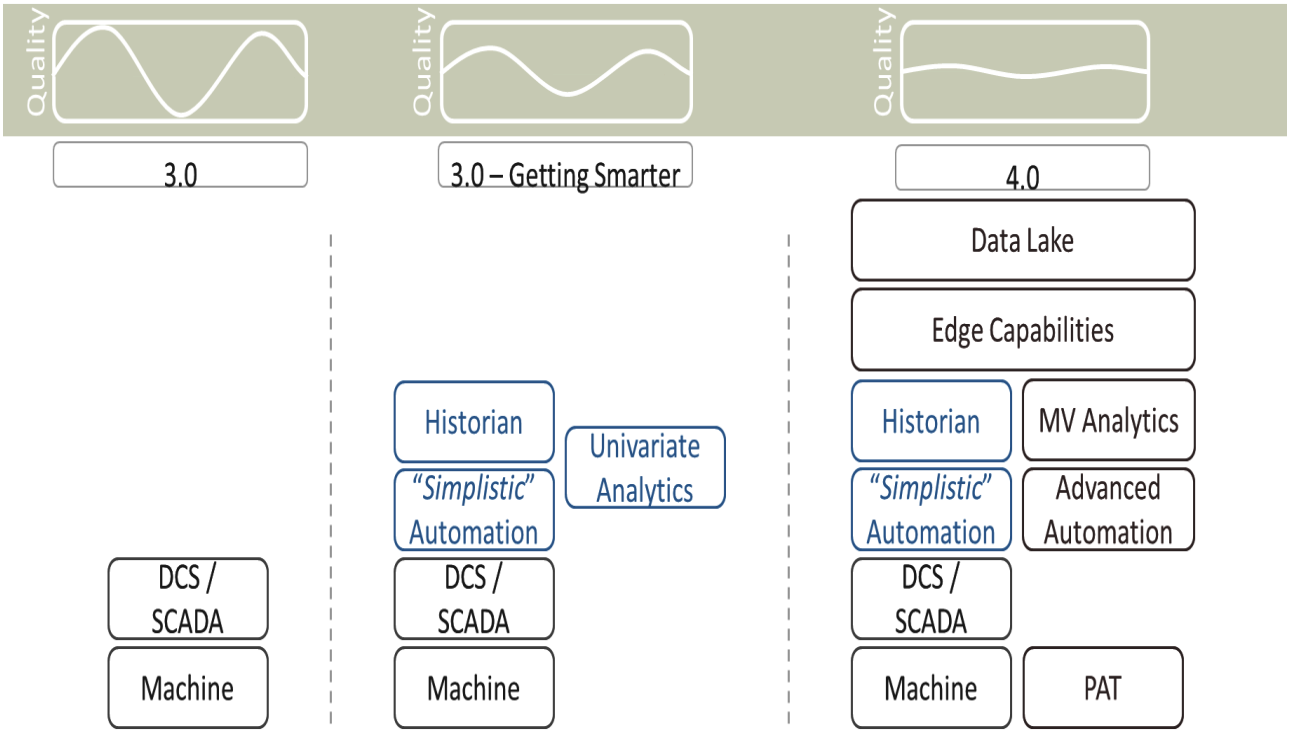

Figure 3: Evolution from Industry 3.0 to Industry 4.0

While data were generated by the machines of the late 20th century, it was difficult to access. It was time and resource consuming to process, and it was disconnected. Process Analytical Technologies (PATs) were isolated, providing an additional non-linked data stream. There was a deficit of the skills requirements in industry to turn all this data into knowledge. Therefore, control was limited.

On the journey to Industry 4.0, the value of data became more apparent. Software programmes were developed to capture process data. These Data historians stored the information in a time series database that could efficiently store data with minimal disk space and fast retrieval. Univariate data analytics became more common place and machines became more automated.

Today the amounts of data being collected and stored is growing rapidly. The real change is in the sheer volume of data that needs to be captured and processed to support 'big data analytics'. This is being driven by increased connectivity of devices and by the introduction of new sensors, as well as by greater awareness of the value of capturing data. Data utilisation is increasing exponentially, and data is being used as a tool for decision-making.

Now, Industry 4.0 connects the industrial internet of things (IIOT) with manufacturing techniques to enable machines to work autonomously without the intervention of a human.

Industry 4.0 to Pharma 4.0 – Smart manufacturing

How does Industry 4.0 relate to the pharmaceutical industry? The term Pharma 4.0 has been adopted by the pharmaceutical industry but what is Pharma 4.0? Pharma 4.0 can mean different things to different people. It can cover the entire supply chain. It can be in relation to personalised medicines, or in relation to predictive maintenance. It can be real-time monitoring of a patient's condition by the physician, and/or it can be Smart Manufacturing.

Smart manufacturing is a broad category of manufacturing with the goal of optimising the manufacturing process. Smart manufacturing is the process that employs computer controls, modelling, big data and other automation to improve manufacturing efficiencies.

Smart manufacturing aims to take advantage of advanced information and manufacturing technologies to enable flexibility in physical processes to address a dynamic and global market.

The Smart Manufacturing concept aligns with ICH Q8, Q9 & Q10 framework. It enables the adaptation of QbD approach to process development and manufacturing. In order to develop a smart manufacturing process/ product it is imperative to understand the relationship between input raw materials, formulation, process performance and product quality, and therefore increase process understanding.

The smart manufacturing approach requires innovative approaches to acquire data – what do we measure? how do we measure it? The measured data are then aggregated and analysed. Data cleaning and Visualisation are critical factors for the success of smart manufacturing. These data can then be turned into process knowledge and the process knowledge turned into process control.

Within a Smart manufacturing platform, processes are robust, reproducible, flexible, scalable and transferable.

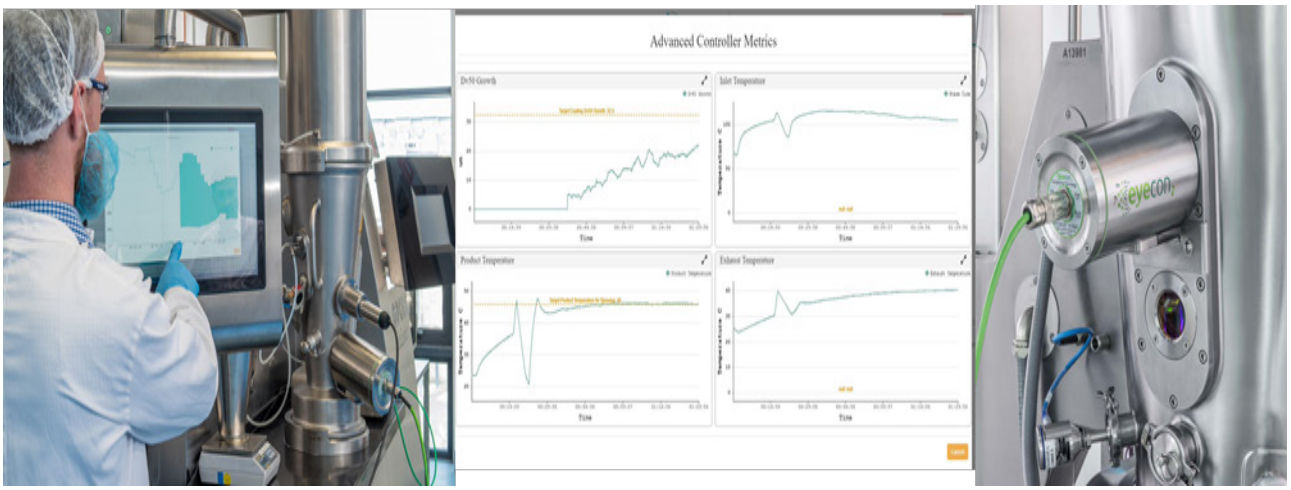

Image 1

2. Why Smart Manufacturing in Pharma?

The pharmaceutical industry is one of the most highly regulated industries in the world. So, is Smart Manufacturing required, or is it an expensive luxury? According to Pharma Times now there were 702 pharmaceutical product recalls in the USA in 2018, almost 2 per day. Of these, the top 5 categories for the recalls were manufacturing related. These top 5 categories accounted for 80% of all recalls. Many markets publish the number of low stocks on any given day. An analysis of this data identifies 'manufacturing issues' to be the main contributor to the low stock levels, at approximately 80%.

These data confirm that there is room for improvement, and that smart manufacturing would improve both quality and supply reliability for the world's patient population which need these products to lead healthy lives.

However, as the saying goes, 'prevention is better than cure', and therefore the most appropriate methodology to the adaptation of the smart manufacturing platform is at the process development stage of a products lifecycle. This strategy is in line with the FDA's 'Guidance for Industry, Process Validation: General Principles and Practices', which encourages greater process understanding at the process development stage (Stage I).

3. Innopharma's Journey to Smart Manufacturing

Innopharma Technology currently develops and implements tools for advanced (4.0) development and manufacturing for powder and solids processes, including in-line real-time sensors, process machine and PAT sensor data alignment and secure storage, data analytics/visualisation, and edge-deployed tools for process logic development and automation with advanced dynamic control.

Innopharma's journey began with the development of a suite of PAT sensors for small molecule final product manufacturing. These technologies evolved over time with incremental improvements based on customer feedback and industry surveys. In 2015 Innopharma began the development of their Smart Manufacturing Technology Platform. This focused-on the fluid bed technologies of Fluid Bed Granulation (FBG) and Fluid Bed Coating (FBC) and was called SmartFBx™.

SmartFBx is an accelerated development and advanced manufacturing platform for Fluid Bed Systems enabling faster more systematic process development and a more robust automated approach to manufacturing. The system aggregates Fluid Bed Process Data, PAT sensor data and other QC analytical or other relevant data as required within a single vertical system. SmartFBx includes the integration of data analytics tools and a module for automation using sophisticated process logic for advanced dynamic control. Selected Batch specific data can also be transferred to EBR/MES, LIMS or other corporate information management and compliance systems. SmartFBx is scalable and can be used to connect multiple new or existing Fluid Bed Systems in development and manufacturing. The platform is suitable for Fluid Bed Granulation, Fluid Bed Drying and Fluid Bed Coating (Wurster). A schematic of the system is presented in **Figure 4**.

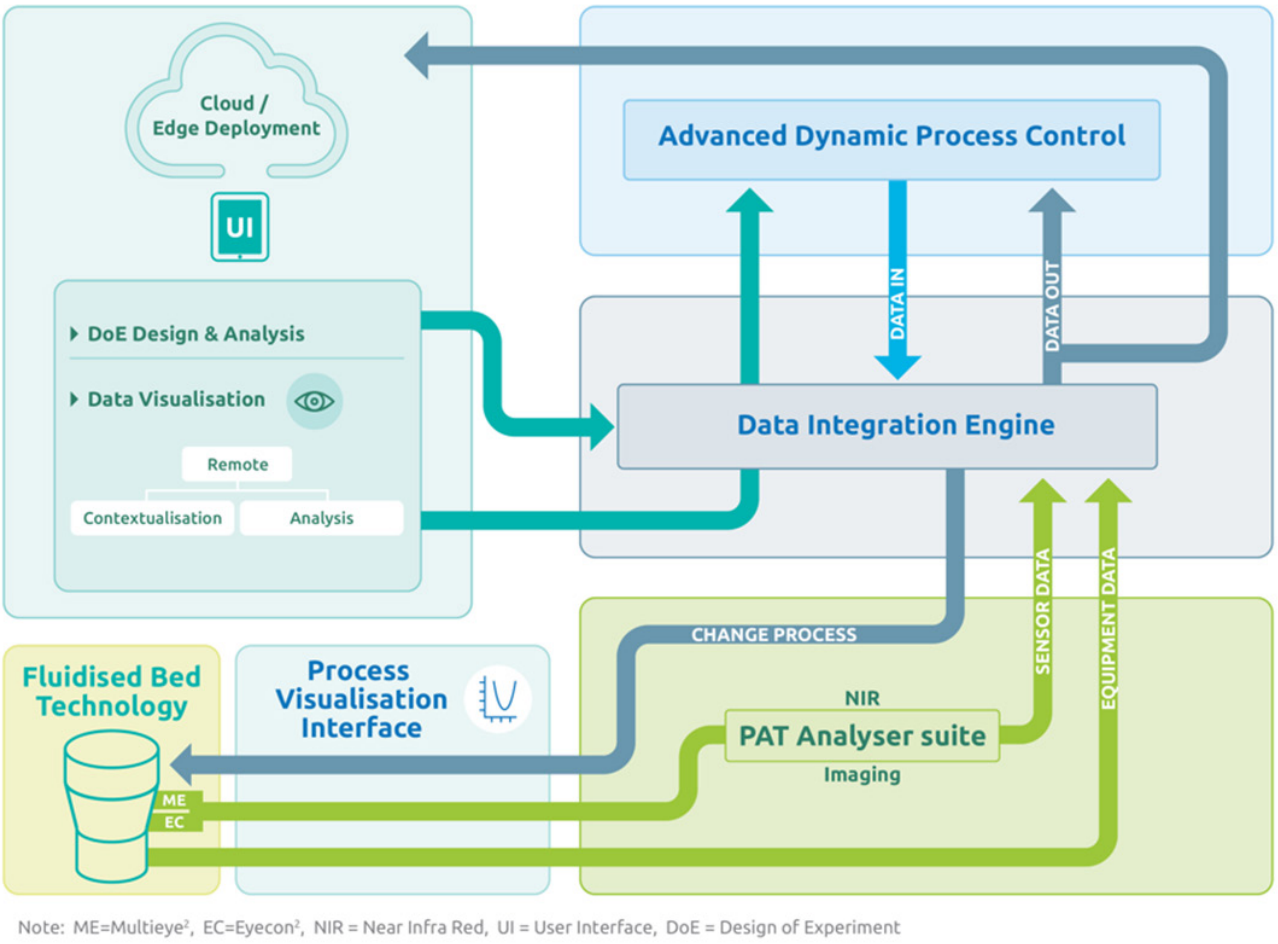

Figure 4: Smart FBx schematic

As well as a manufacturing workflow, a need exists in Lab Scale Process Development for more consistent, reproducible and compliant execution of DOEs within a development workflow. Innopharma's vision of Intelligent Batch Manufacturing lends itself to addressing this need by providing workflows within a HMI to facilitate a fully digitised Quality by Design (QbD) approach to design space definition and edge-of-failure analysis through automated DOE execution. The automated collation, contextualisation, visualization and sharing PAT and process data, results in a faster development process and can significantly reduce lead time to market.

The technology provides process intelligence that helps users gain a specific understanding of their manufacturing processes, how to control their sources of variability, or the impact of this variability through powerful analytics and advanced dynamic process control.

The addition of such digital technology to lab scale FB systems adds value for customer by enabling faster process development lead times and tech transfer thus enabling the customer to take a more Industry 4.0 approach to QbD and DoE.

4. RISK Reduction – Smart Manufacturing

While Smart FBx controls fluid bed technologies, the same architecture can be applied horizontally across the other technology platforms associated with small molecule final product manufacturing. Sensors are available that can be integrated with each stage of the manufacturing process to measure appropriate CQAs as illustrated in Figure 5.

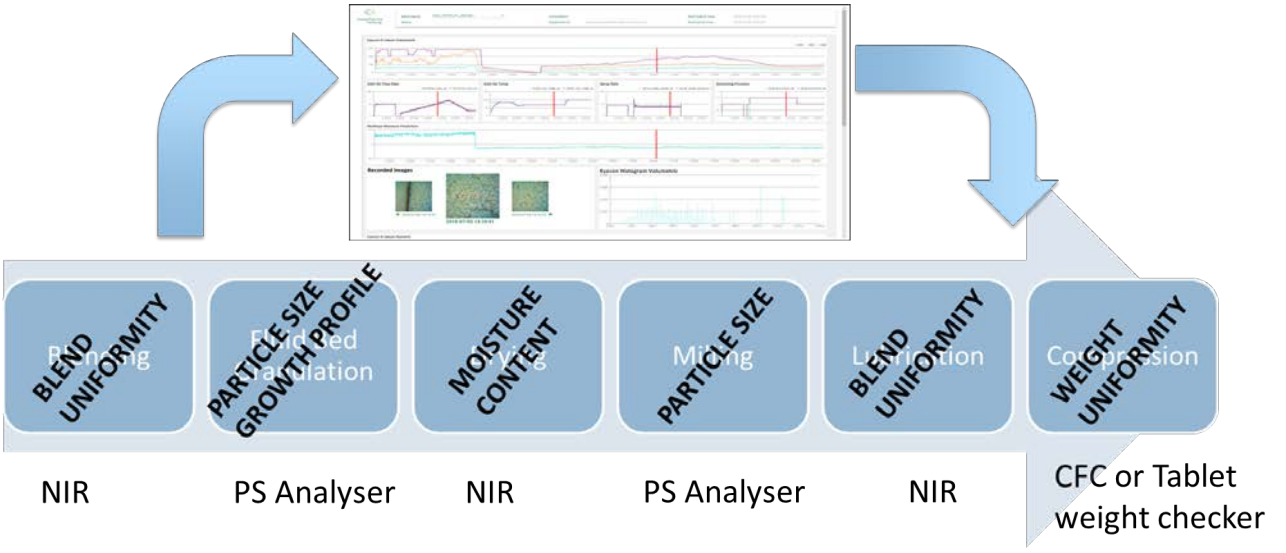

Figure 5: OSD Smart Manufacturing

The ultimate goal and total adaptation of smart manufacturing is to control each stage of the manufacturing process and subsequently digitally connect each stage together on a product-by-product basis. However, this is a marathon rather than a sprint. Manufacturing plants may adopt an iterative and incremental approach on their smart manufacturing journey. Their approach should be based on risk to the patient, implementing a strategy of reducing risk along the journey. The end of the journey will result in processes that are robust, reproducible, flexible, scalable and transferable. This in turns translates into medicines that are safer and more affordable.

5. Knowledge management

Knowledge management may be defined as 'efficient handling of information and resources within a commercial organization'. It is no secret that in a paper-based world, knowledge management is an enormous challenge. Batch manufacturing and testing information is filed away for a definitive time period before being shredded. Numerous process development reports, from the initial development work, through product lifecycle activities such as, raw material changes, investigations, process improvements etc are generated and filed. Hard copy validation reports are generated and filed. While the hard copy material is available in archives, document control systems and Managers' offices, the knowledge typically resides with the

individuals who generated the documents. Therefore, knowledge tends to be managed by a 'Who do I need to ask?' approach rather than a systems-based approach. Employee retention becomes a major source of knowledge management. However, *employee retention has become an increasing challenge for employers as we are currently in an employee-driven market, and this trend is likely to continue to accelerate as the world's economies continue to grow*.

To compound this issue, many companies have manufacturing facilities in numerous countries around the world. The same products may be manufactured at different locations supplying different markets. For these companies, valuable information that should be shared across the network is also lost.

A huge opportunity to manage knowledge is achievable with the deployment of smart manufacturing across a company's network, as illustrated in **Figure 6** below.

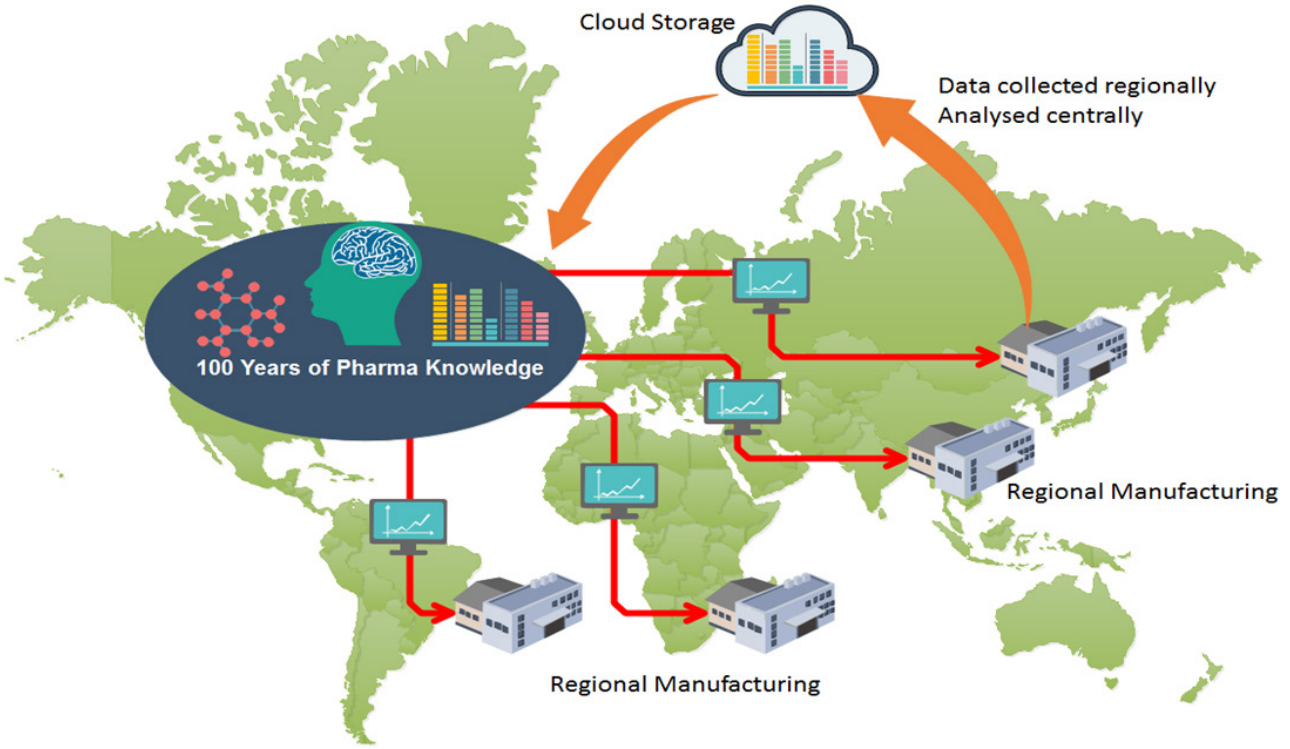

Figure 6: Knowledge Management Network

With Smart Systems integrated within the site network, large volumes of data generated can be converted into information/knowledge for each batch manufactured. This knowledge can be accumulated on a batch-by-batch basis which leads to greater overall process understanding, and in turn to better process control.

Better knowledge management will enhance the overall QMS. It will facilitate the generation of APQRs in a timely manner, eliminating the need to trawl through reams of batch documentation. It will facilitate the early detection of issues and lead to more efficient investigations. Not only can this knowledge be available to the manufacturing site, it can also be available across the network. Many organisations have developed central technical services groups supporting the entire network rather than local technical services groups

supporting their own site. The success of this model is based on the ability to access and analyse all the required data easily.

Smart manufacturing will lead to more reliable supply chain, reduced inventory, better quality, enhanced safety and more affordable medicines for the world's patient population.

6. Conclusion

The main benefits of Smart Manufacturing are in the areas of productivity, quality and speed. Increased productivity will be achieved through a higher level of automation that reduces production time. This in turn enables better asset utilisation, better resource utilisation and better inventory management. Increased quality is achieved through the continuous monitoring, in real time, of CQAs via sensors and the ability to intervene in case of deviation from the norm in order to bring the process back in control. This in turn eliminates time spent performing rework activities and also significantly reduces time spent on investigations. From drug discovery to commercialisation, speed to market is a critical success factor for any business. Smart manufacturing adds value for the customer by enabling faster process development time and tech transfer, and can significantly reduce lead time to market.

Overall, Smart Manufacturing will lead to more reliable supply chain, reduced inventory, better quality, enhanced safety and more affordable medicines for the world's patient population. Therefore, Smart Manufacturing plays a major role in enabling QRM & KM to realise safer and more affordable medicines for patients in the 21st Century.

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Part 5: Pharmaceutical Regulatory Science Team (PRST) contributions

5.1 Knowledge Management: Advancing the dialogue to improve patient outcomes through improved knowledge transfer

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1. Introduction

While knowledge management (KM) has been widely applied in other industries, the international biopharmaceutical industry has struggled with the meaningful and sustained application of effective KM practices. This paper will highlight recent research to further explore this issue and describe the next phase of research by the TU Dublin Pharmaceutical Regulatory Science Team to further define the barriers to improved KM and how the industry might improve.

2. Background

In 2008 The International Council for Harmonisation (ICH) published a guideline on Pharmaceutical Quality System Q10 [1], commonly referred to as 'ICH Q10.' The objectives of ICH Q10 are:

i. to achieve product realisation
ii. to establish and maintain a state of control
iii. to facilitate continual improvement.

ICH Q10 positioned knowledge management (KM) as an enabler to the Pharmaceutical Quality System (PQS) (**Figure 1**) suggesting that effective knowledge management is required to realise an effective PQS, and therefore to achieve the objectives of ICH Q10. This regulatory guidance marked the first time that knowledge management was identified as an expectation for the industry. However, minimal guidance on what was required, or how this might be achieved, was provided in ICH Q10. Although the industry has struggled with KM adoption, no further guidance has been published in the 10 years since the release of ICH Q10. The ICH Q10 Committee did intentionally set expectations for what KM was *not* to be [2] including it was not viewed as a requirement to be solved by an information technology (IT) system. Rather, the 'what' and 'how' for KM were left up to individual organisations. But no further guidance, such as models for best practices, guiding principles, or measures of progress or realisation, were provided. Perhaps this is a contributory reason as to why progress in KM has been slow and elusive in the industry.

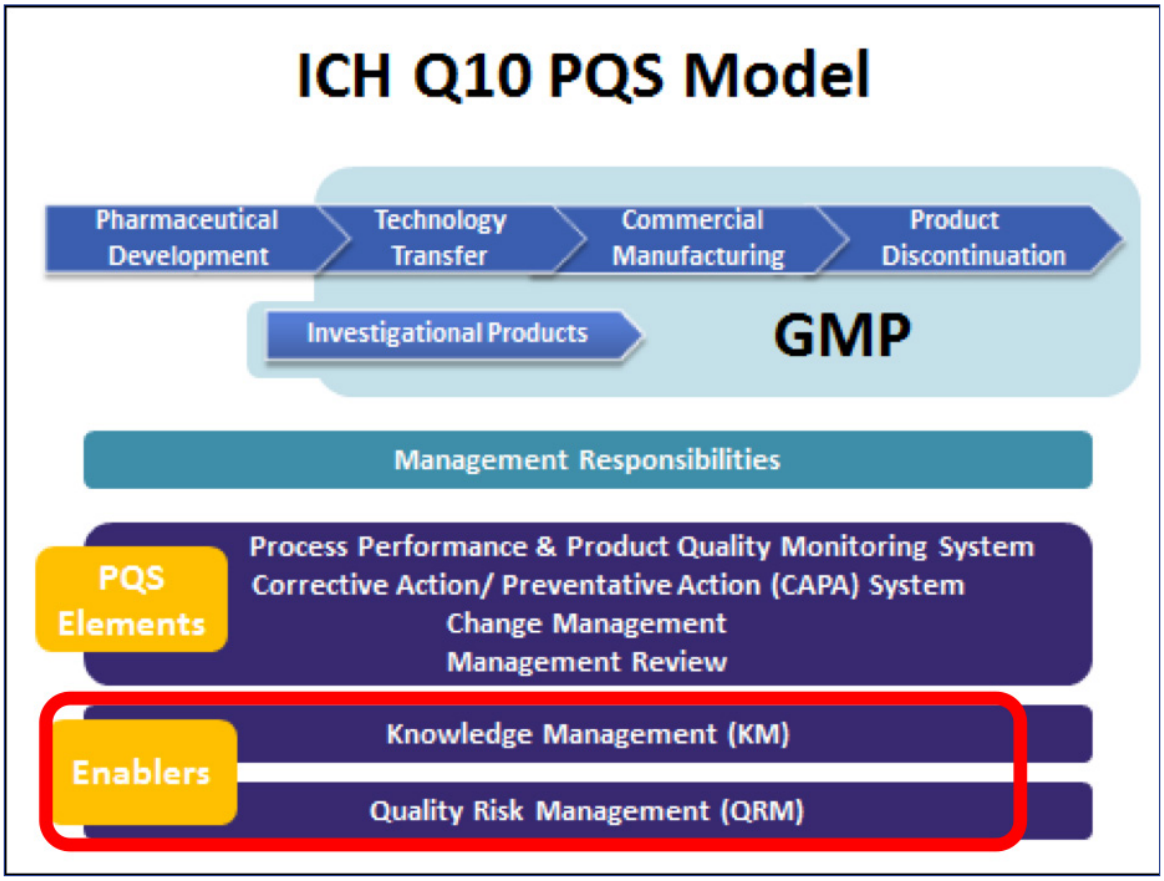

Figure 1: ICH Q10 Pharmaceutical Quality System

Formal research on knowledge management in the biopharmaceutical sector was undertaken by Kane in 2014 [3]. At the commencement of her research in 2014, little guidance existed to describe how KM might actually enable a more effective pharmaceutical quality system. Kane's research has led to the establishment of a foundation for KM in the biopharmaceutical industry. This foundation, known as the *Pharma KM Blueprint*, **Figure 2**, consists of four key elements to begin to bridge the gap from KM theory to practice, as follows:

i. **Managing Knowledge as an Asset**. A foundational principle established through the research which addresses the need to value and maintain *knowledge assets* in the same way as physical assets within an organisation.

ii. **Pharmaceutical Product Knowledge Lifecycle Model**. A model to address the challenge of enabling *knowledge flow* in order to increase visibility, access and use of product and process knowledge assets across the product lifecycle. Specifically, this model asserts that the lifecycle model for a pharmaceutical product as depicted in ICH Q10 [1] may put too much emphasis on the initial technology transfer for a product, i.e. the technology transfer from *product development* into *commercial manufacturing*, and fails to acknowledge the multiple technology transfers that typically occur over the life of product, especially in today's globalised marketplace and with the extent of contract manufacturing. Further, this technology transfer emphasises the transfer of *technology* but does fully address the transfer of *knowledge* that must also occur.

iii. **House of Knowledge Excellence Framework**. A framework for a systematic KM programme linked top-to-bottom with the strategic objectives of an organization. This framework consists

of KM practices, pillars (people, process, technology, governance), and KM enablers to support the effective management and flow of knowledge assets. This comprehensive framework can be leveraged to assess gaps in how an organisation is deploying KM.

iv. **Knowledge Management Effectiveness Evaluation**. A practical KM diagnostic tool which may be used to identify and evaluate areas of opportunity and to track progress on closing knowledge gaps, and overall KM maturity of an organization. The diagnostic can be repeated to demonstrate improvement in KM maturity over time.

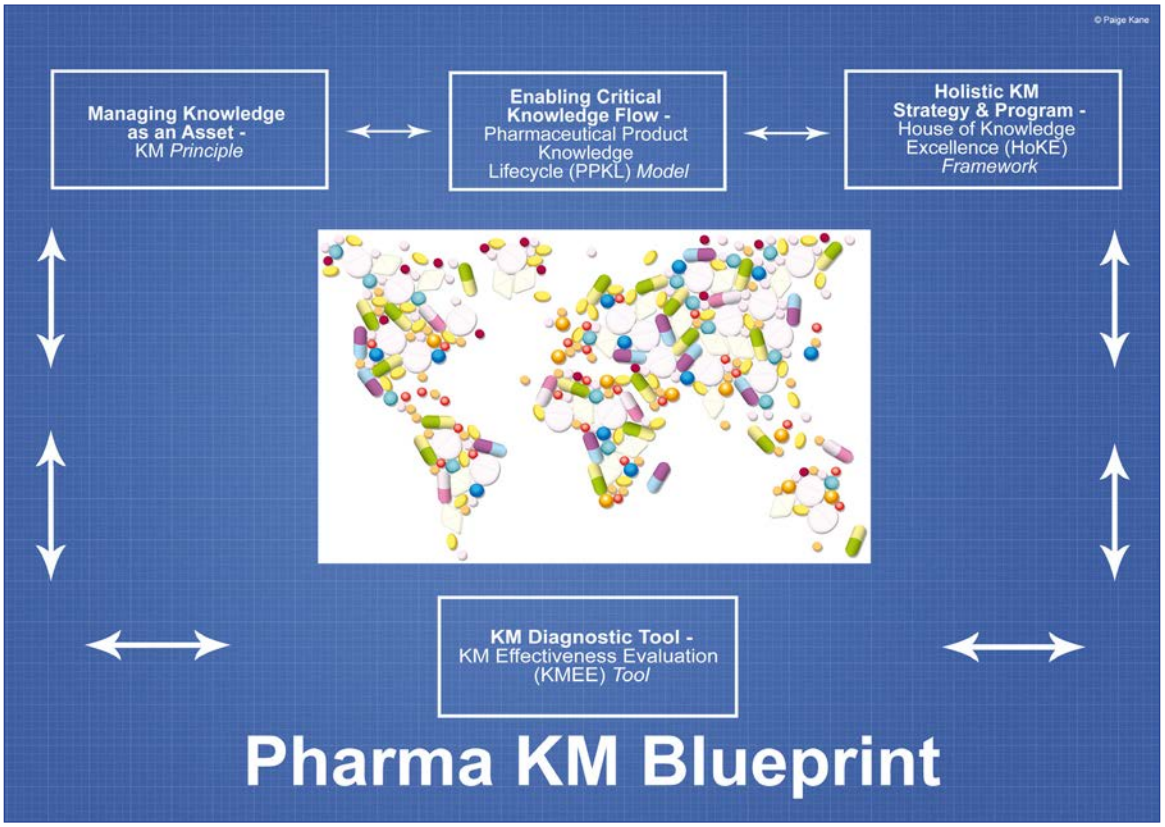

Figure 2: Pharma KM Blueprint

Another development in the industry is the expected issuance of new guidance by ICH, Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management, Q12 [4], commonly known as ICH Q12 (at the time of this paper, in draft version under public consultation). The ICH Q12 guideline is expected to further advance the expectation that improved product and process knowledge can contribute to a reduction in the number of regulatory submissions, and that accumulated knowledge gained during development and implementation of changes is expected to be applied to manage risks to product quality. These expectations will further increase the importance and urgency for the industry to be more effective at the practice of knowledge management.

3. Technology transfer's dependency on knowledge transfer

A key guidance document, the PDA Technical Report No. 65 on Technology Transfer [5], states 'technology transfer can affect drugs and patients', clearly highlighting the importance of an effective technology transfer to ensure product outcomes and to protect patients.

The literature suggests it is abundantly evident that knowledge, including effective transfer of knowledge, is vitally important to successful technology transfer. We know from Millili [6] that insufficient process knowledge results in a poorly scaled-up process, along with other undesirable outcomes including:

- Non-robust processes (decreased process capability, i.e. Cpk)
- Decreased reliability
- Reduced production rates
- Increased number of atypical (e.g. defects, elegance issues, etc.)
- Difficulty handling variations (raw materials, process controls, …)
- Inefficient validation.

However, a preliminary review suggests the industry is not always doing well with transferring knowledge during technology transfer. There is clearly an opportunity for improvement. Consider the following issues and shortcomings cited on knowledge transfer effectiveness during technology transfer:

- "…assays were transferred but the sending party did not provide complete information and some of the information was out-of-date…" [7]
- "…poor process understanding, coupled with incomplete documentation (i.e. codification) of all the required process parameters…" [8]
- "The third mistake is not arranging for scientist-to-scientist interaction during the transfer process. Scientists from similar departments at both the transferring company and the receiving company need to get acquainted, understand the transfer process, and then work side by side at the bench or in the plant. Without that personal interaction, your transfer is risky" [9]
- "…incomplete knowledge transfer…is a consistent problem…" [10]
- "…there was no master document to track all the information and it was sent out piecemeal to different points of contact…" [7]
- "…providing incomplete information about the nature of the biopharmaceutical or protein molecule such as its properties, its activities, and its stability under different conditions. Often, companies know this information, but don't pass it on…" [9]

4. New Research to Advance Knowledge Transfer, Understanding and Effectiveness

Given the clear importance of effective knowledge transfer to enable successful technology transfer and associated outcomes, and preliminary signals suggesting poor performance by the industry, this presents an opportunity for further research on this topic. Building on the foundational research established by Kane, and

the advancing expectation to better manage product and process knowledge highlighted in Q12 [4] and other business contexts [11], further research will be undertaken by Lipa. This next phase will advance knowledge management research with a deeper focus on product lifecycle knowledge, specifically on technology transfer. The research will explore elements of both explicit and tacit knowledge transfer. Lipa's preliminary research hypothesis is as follows:

i. The industry **does not have a holistic end-to-end view of what it knows about its products** across the product lifecycle, **nor how to best ensure this knowledge 'flows'** to ensure the best possible product outcomes. These outcomes include product realisation through a readily available, cost effective and high-quality product to patients, as well as additional outcomes of operational efficiency and a workforce that has the knowledge it needs to do its best work.

ii. Further, **tacit knowledge is critical but is not effectively managed or transferred** during key activities in the product lifecycle, including key processes such as technology transfer.

In order to raise awareness and to provide guidance on how to improve knowledge transfer associated with technology transfer, and to ultimately improve technology transfer outcomes, this research intends to:

a. Characterise the current state of how KM enables technology transfer, including perceived importance and effectiveness for each explicit and tacit knowledge.

b. Benchmark other industries on processes and proven effectiveness of knowledge transfer.

c. Develop a model to describe the maturity of knowledge transfer.

d. Develop recommendations for enhancing knowledge transfer during technology transfer, including any supporting tools, assessments or models to accelerate post-research uptake.

Lipa's research commenced in October 2018, and its intent was shared at *An Audience with Regulatory, Academia and Industry on The Role of Effective QRM & KM in Product Realization for Patients in the 21st Century* on 04 April 2019 at Technological University Dublin. During this seminar, the audience was polled by Lipa for their perspectives on the importance and effectiveness of knowledge transfer to enable an effective and efficient technology transfer, as an opportunity to gather perspective and further validate the research direction. The balance of this paper reports a summary of the findings from this poll and other research conducted since the seminar and frames the next steps for the research.

5. Results: Audience Poll on Knowledge Transfer Enabling Successful Technology Transfer

Fifty-six (56) responses were received. The poll started with a question to characterise the level of experience attendees had with technology transfer, with options including **none / no experience, limited experience, good experience, very experienced**. No fixed definitions were provided, the participants were allowed to select their experience according to the choices provided, and subsequent survey results are presented in this context. It is important to note that all results from this survey are considered directional in nature only

due to the qualitative nature of the questions provided, although useful comparisons can be made within the response data.

The second question asked, "To what extent do you agree **knowledge transfer** is a critical component of an **effective and efficient technology transfer**?" to gauge overall perception of the role of knowledge transfer as part of technology transfer. Responses were on a numerical scale, ranging from (1) to (5), with a reply of (1) indicating *strongly disagree*, to a reply of (5) indicating *strongly agree*. This and all subsequent questions included an option of n/a or prefer not to answer so respondents had a chance to opt out on any question and therefore not counted in the response summary.

The results are depicted in **Figure 3** as numerical averages of the responses, and indicate **strong agreement that knowledge transfer is important** to an effective and efficient technology transfer, regardless of technology transfer experience level. Interestingly, recognition of the importance of knowledge transfer **positively correlates with level of experience**, suggesting this understanding may be under-appreciated by those not as familiar with technology transfer. Also, the extent of agreement increased, i.e. the range of answers decreased, with increasing experience (not shown). For the 'very experienced' respondents, all respondents reported 'strongly agree' (i.e. unanimous agreement that knowledge transfer is critical to technology transfer).

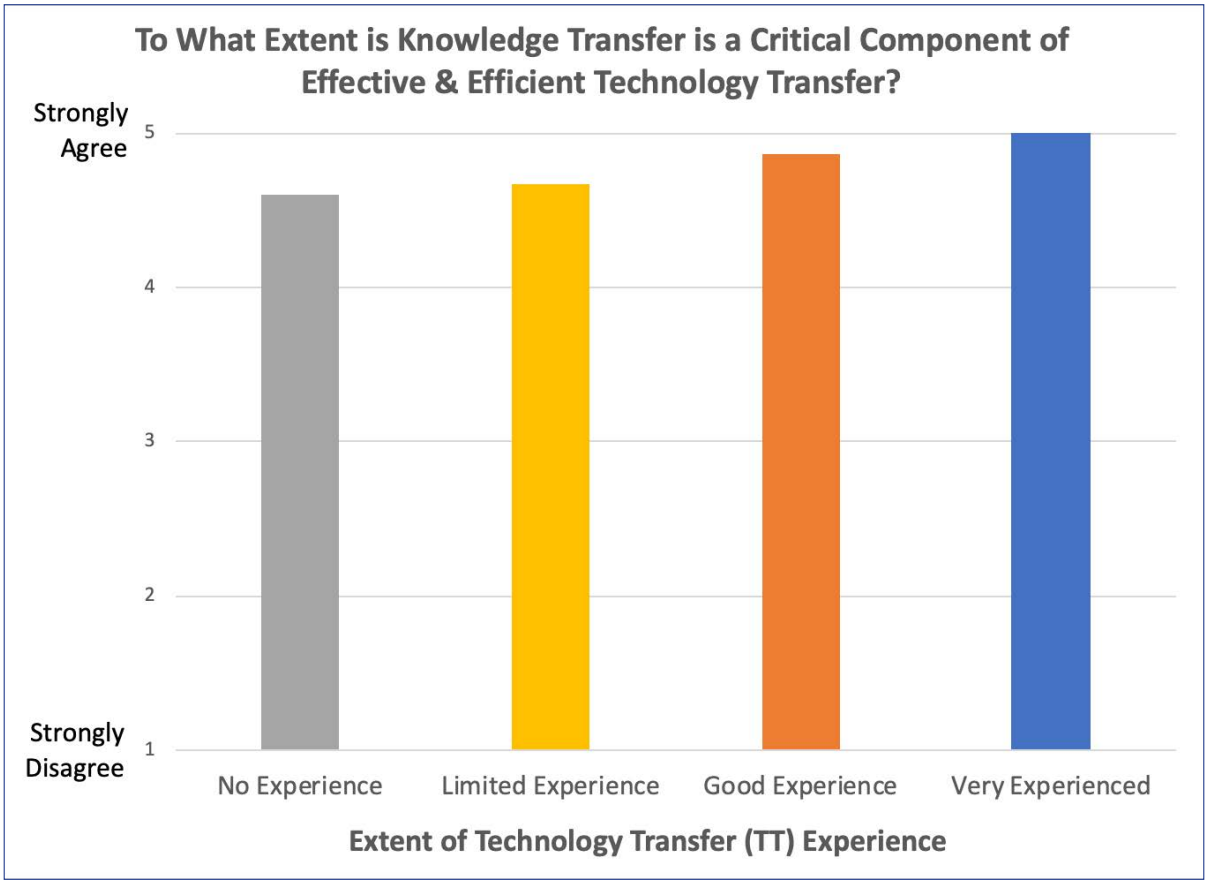

Figure 3: Importance of Knowledge Transfer to Technology Transfer

The next questions deconstructed knowledge transfer down to the sub-types of explicit knowledge transfer, and tacit knowledge transfer. Explicit knowledge was defined as documents and other 'codified' knowledge that takes no explanation or dialog to fully understand. Tacit knowledge was defined as *knowledge associated with experience, subject matter expertise, decision rationale, observation, undocumented history and other knowledge "in people's heads."*

Specifically, the questions asked, "To what extent do you agree **transfer of explicit knowledge** is a critical component of an **effective and efficient technology transfer**?", followed by the same question focusing on **tacit** knowledge. Responses were on a numerical scale, ranging from (1) to (5), with a reply of (1) indicating *strongly disagree*, to a reply of (5) indicating *strongly agree*. The results are depicted in **Figure 4**, and are included only from the very experienced cohort both acknowledging this group would have the best-informed opinion. The results indicate strong agreement **each explicit and tacit knowledge is critical** to an effective and efficient technology transfer. Further, the relative criticality for each explicit and tacit knowledge transfer to effective and efficient technology transfer is generally similar.

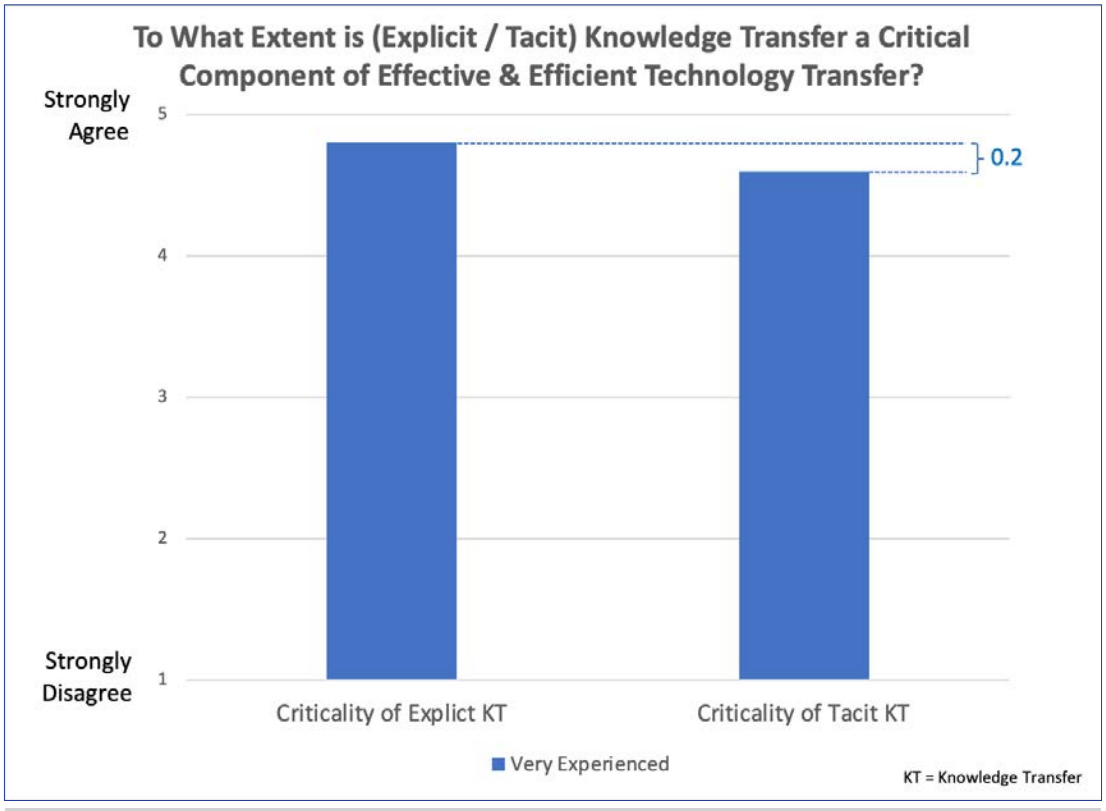

Figure 4: Explicit and Tacit Knowledge Importance to Technology Transfer

The next question asked about *effectiveness* of *explicit* knowledge transfer, specifically, "How **effective** do you feel **transfer of explicit knowledge** is for a typical technology transfer?" Responses were on a numerical scale, ranging from (1) to (5), with a reply of (1) indicating *not effective at all*, to a reply of (5) indicating *highly effective*. Results are depicted in **Figure 5**. Also included is **Figure 5** is the result from the previous question on

the criticality of explicit knowledge transfer so a comparison between criticality and importance can be made (In other words, a qualitative evaluation of the question "Given it's criticality, how effective are we at doing it?"). The results suggest that although explicit knowledge transfer is deemed critical, the **effectiveness of explicit knowledge transfer is only marginally effective**. The difference between criticality and effectiveness (1.4) is noted for later comparison with the same evaluation for tacit knowledge.

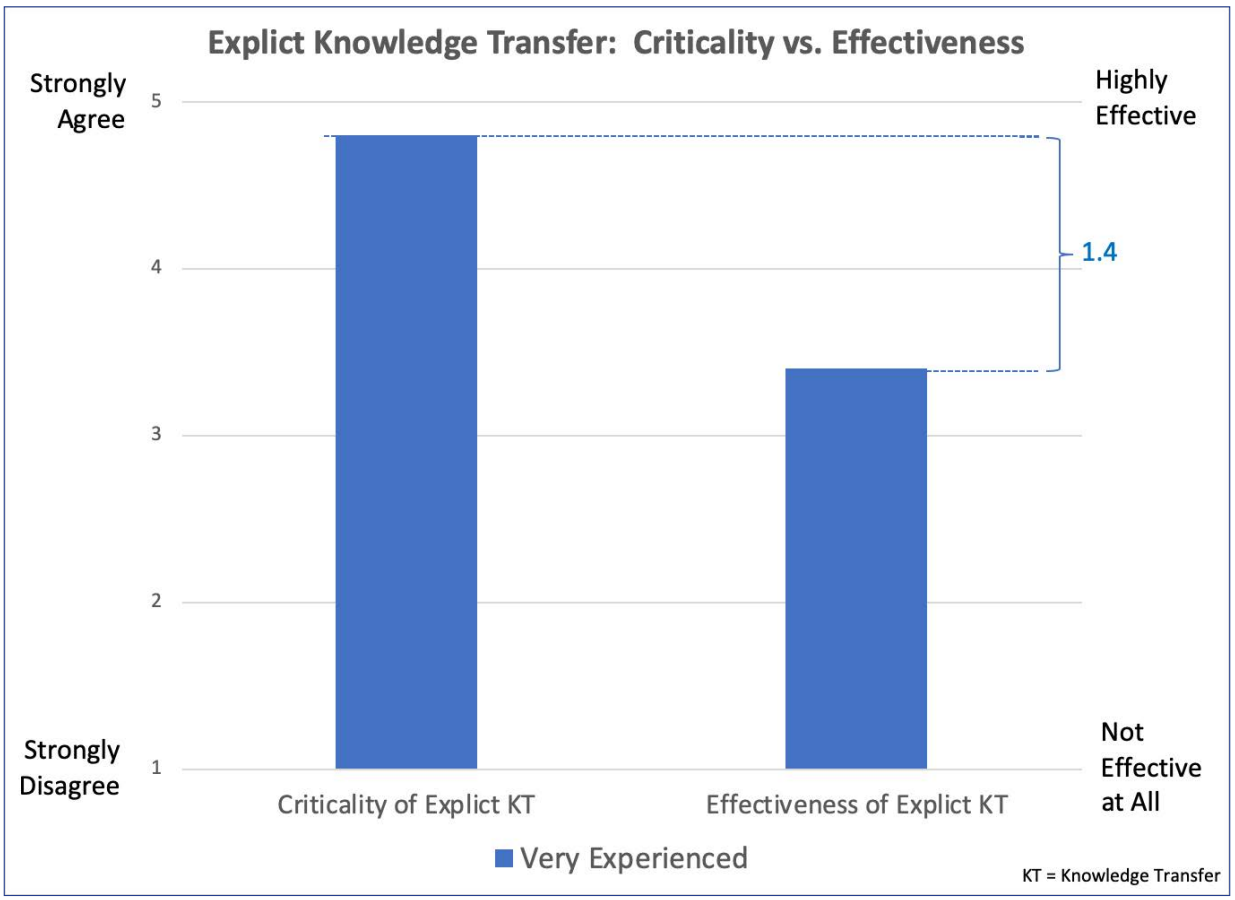

Figure 5: Explicit Knowledge Transfer: Importance vs. Effectiveness

The same question was asked to evaluate tacit knowledge transfer effectiveness, "How **effective** do you feel **transfer of tacit knowledge** is for a typical technology transfer?", with the same response options. Again, the previous criticality result is included for comparison (**Figure 6**). The results indicate tacit knowledge transfer effectiveness is somewhat ineffective (average result = 2.0) and is significantly lower than the effectiveness of explicit knowledge transfer (average result = 3.4). When effectiveness is compared to criticality, the gap is significantly bigger than that noted for explicit knowledge (delta of 2.6 for tacit vs. 1.4 for explicit).

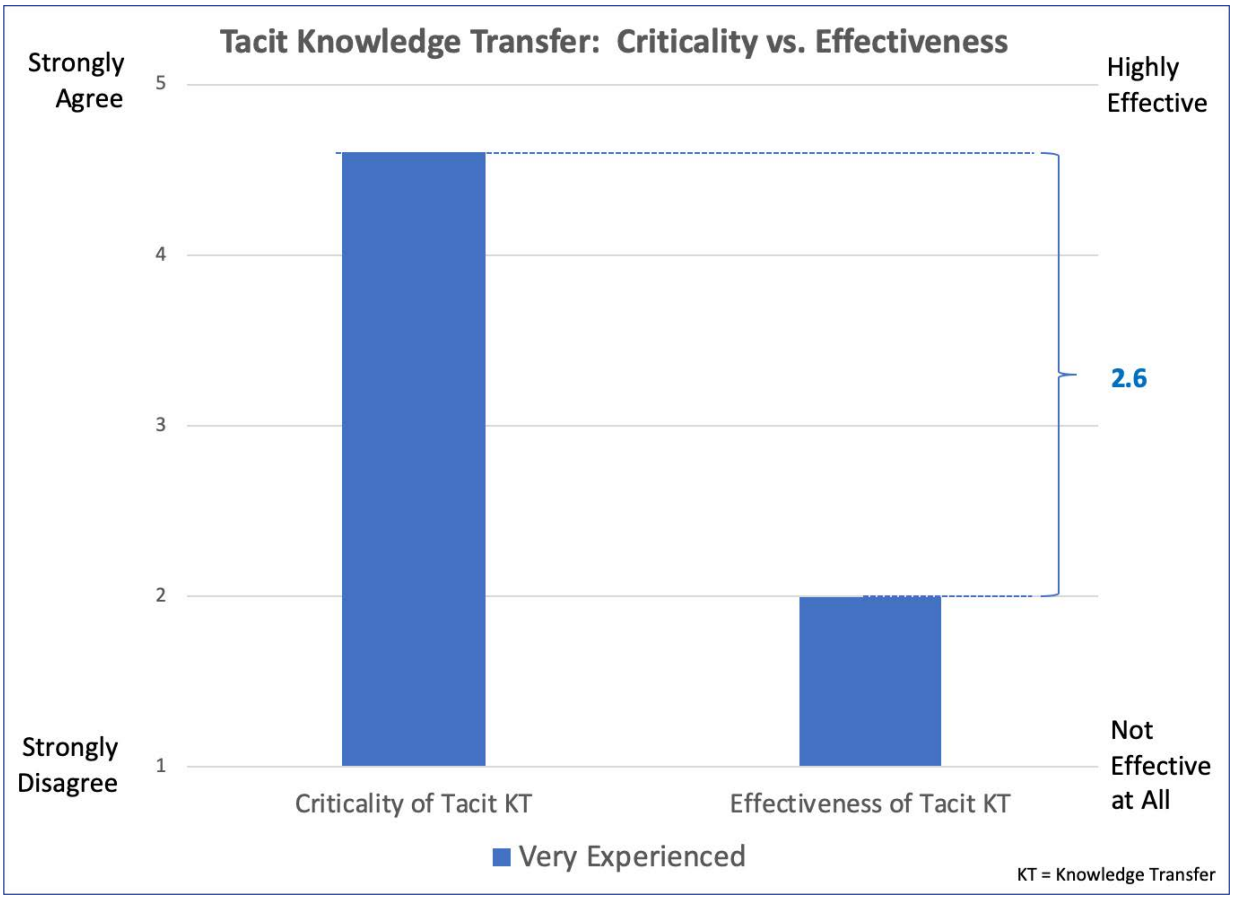

Figure 6: Tacit Knowledge Transfer: Importance vs. Effectiveness

Another interesting insight lies in examining perspectives across the experience levels captured during the first question. Similar to recognition of overall knowledge transfer importance (as noted previously in **Figure 3**), the importance of tacit knowledge transfer generally increases with experience level (blue line in **Figure 7**). However, the respondent's assessment of *effectiveness significantly decreases with experience level* (orange line in **Figure 7**). The perspectives of increasing importance with decreasing effectiveness suggests appreciation of the importance of tacit knowledge transfer is hidden and under-appreciated. In other words – the more one knows, the more one realises tacit knowledge transfer is really important, but that the industry really isn't very good at it!

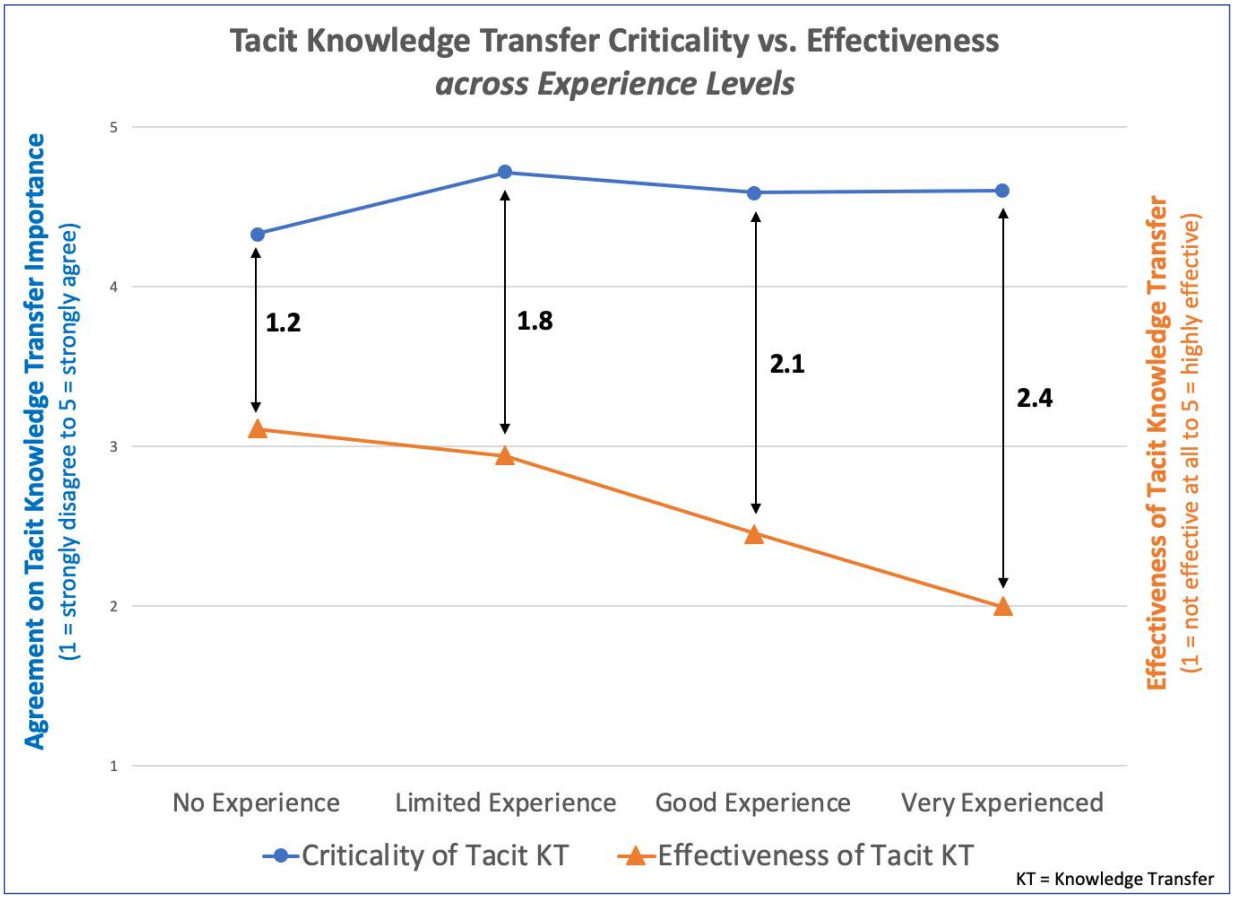

Figure 7: Tacit Knowledge Perspectives across Experience Levels

Although only directional in nature, these poll results further validate the importance of knowledge transfer to technology transfer outcomes, for both explicit and tacit knowledge transfer. In particular tacit knowledge transfer is viewed as ineffective yet very critical, so any advances in this domain will benefit technology transfer outcomes, and ultimately benefit patients.

6. Knowledge Transfer Prevalence in Industry Guidance

Additional research since the seminar included a review of common industry guidance on technology transfer, to assess the extent to which kno**wledge transfer**, **knowledge management** and **tacit** knowledge concepts are presented and explained, along with the extent of illustrative examples and guidance or tips on the 'how'. The following technology transfer guidance was reviewed, and the frequency of these concepts was tabulated and summarised in **Table 1**.

- WHO Guidelines on Transfer of Technology in Pharmaceutical Manufacturing [12]
- ISPE Good Practice: Technology Transfer, 2nd Edition [13]
- ISPE Good Practice: Technology Transfer, 3rd Edition [14]
- PDA Technical Report, No. 65, Technology Transfer [5]
- PDA Tech Transfer Interest Group Report Out, PDA 2019 Annual Meeting (presentation) [15]

A qualitative assessment was conducted on how well these guidance documents introduced the knowledge transfer concepts above, including how well they are collectively **explained**, whether they **provided illustrative examples**, and whether they **provided guidance / tips on 'how'**. These results are also provided along with author commentary in **Table 1**.

				Frequency of Terms			How well these terms are collectively...			
Organization	**Technology Transfer Guidance Document**	**Year of Issue**	**Length in Pages**	***Knowledge Transfer***	***Knowledge Management***	***Tacit*** (Knowledge)	**Explained**	**Illustrative Examples Provided**	**Guidance / Tips on How provided**	**Observations by Author**
WHO	WHO Guidelines on Transfer of Technology in Pharmaceutical Manufacturing	2011	25	1	1	0	Little to None	Little to None	Little to None	Single reference, brief introduction to concepts.
ISPE	Good Practice Guide: Technology Transfer (Second Edition, *superseded*)	2014	81	12	4	5	Limited	Limited	Little to None	Solid references to the importance of KT and KM, and how successful TT is dependent. Tacit concept introduced.
ISPE	Good Practice Guide: Technology Transfer (Third Edition)	2018	152	21	13	14	Good	Good	Limited	KM cited as a driver for the update, strong guidance on the importance of underlying knowledge. Solid examples for tacit knowledge. Some simple examples of how but examples are high level or conceptual only.
PDA	Technical Report No. 65, Technology Transfer	2014	61	0	3	0	Little to None	Limited	Little to None	Brief introduction to concept of KM, but little beyond high level concepts linked to ICH Q10.
PDA	PDA Tech Transfer Interest Group Report Out, 2019 Annual Meeting (presentation)	2019	n/a	yes	yes	no	Limited	Limited	Little to None	Included as this was a recent development and may lead to a revision to PDA TT Technical Report, and/or a Technical Report on KM. KM focus appears exclusively document centric, no mention of tacit knowledge or related concepts. Inventories provided by type but concepts of KT / KM not well explained.

Terms: TT = Technology Transfer; KT = Knowledge Transfer; KM = Knowledge Management

Table 1: Summary of Guidance citing Knowledge Transfer as an Enabler to Technology Transfer

On review of these guidance documents and the summary created above, the following are observations shared by Lipa. In general:

i. Technology Transfer guidance is often very '**document-centric**' (i.e. focused on explicit knowledge)

ii. Knowledge management, mostly around explicit knowledge, is called out in guidance but is **very vague** in what it means:

   » Little for supporting principles or guidance on how to do it effectively

   » Starting to change in places…but perhaps still not enough or fast enough.

iii. 'Tacit' knowledge is not often well recognised as a source of knowledge, nor is there guidance on how to do it effectively.

iv. Technology Transfer risks of failure **do not acknowledge** concepts **of insufficient knowledge transfer or availability**.

For ISPE guidance, the second edition of the Good Practice Guide was included as a baseline to compare against the third edition, to evaluate any changes over time. The third edition [14] lists five areas of highlight for the revision, one of which is "Recognition that knowledge management is a critical component of effective technology transfer…". It is clear in the results summarised in **Table 1** the presence of KM and related concepts has been significantly strengthened beyond a starting baseline from the second edition.

For PDA guidance, the PDA Tech Transfer Interest Group at the 2019 PDA Annual Meeting in March 2019 in San Diego, California, shared the results of a recent survey on Technology Transfer [15]. Lipa attended the session where the PDA Tech Transfer survey results were shared. The survey was intended to assess the current practices and future needs for improving the Technology Transfer process. The survey covered:

- Demographics
- Types of Technology Transfer Performed
- The Technology Transfer Process
- Use of Multi-Disciplinary Teams
- Technology Transfer Tools
- Challenges.

The results indicated that KM would be an area where additional PDA guidance would be helpful. The subsequent discussion on KM in session focused heavily on a '*master plan*' for knowledge management which primarily focused on documents and information. Also, a set of KM "soft skills" was identified as required, although in the opinion of Lipa, these are primarily good business communication and team leadership skills, rather than traditional KM skills as described elsewhere [16].

In general, across any of the guidance documents, there does not appear to be a measure for the effectiveness or completeness of knowledge transfer associated with technology transfer, with the exception of document turnover lists. This will be further investigated during subsequent research.

7. Conclusion

In conclusion, KM is still a relatively immature practice in the biopharmaceutical industry, especially when compared to Quality Risk Management, Change Management and other practice domains. The need for improved KM is evident, not only because of expectations found in regulatory documents or industry guidance, but because there is a need to act – to better manage knowledge – in the best interests of the patients. This is first and foremost to protect the patient through availability of a high quality, cost effective product, but also other business drivers which ensure the continued competitiveness of the organizations in the industry [11]. Research by Kane between 2014 and 2018 has helped establish a baseline for the importance of knowledge to the biopharmaceutical industry, and to manage this knowledge as an asset. The next phase of research

by Lipa as introduced in this paper is intended to further provide tangible evidence of the need for KM and practical advice to help the industry apply good KM practices to improve technology transfer outcomes. The initial findings presented within this paper well justify the planned efforts in this area.

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5.2 Biopharmaceutical Manufacturing Quality Risk Management
A Role-Based Competencies Model

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1. Introduction

In October 2018 the Pharmaceutical Regulatory Science Team (PRST) at the Technological University Dublin (TU Dublin) Ireland hosted a seminar with Regulatory Science Ireland (RSI) and with the Health Products Regulatory Authority (HPRA) titled: *An Audience with International Regulators in the Manufacture of Medicines: Quality Risk Management (QRM) and Knowledge Management (KM)*. In that seminar I had the opportunity to share with the audience the focus of my doctoral research regarding developing Quality Risk Management Standards as professional standards for QRM practitioners which includes role-based technical and behavioural competencies.

My original research questions were as follows:

1. What individual responsibilities must there be in pharmaceutical manufacturing to achieve QRM effectiveness?
2. What are the competencies associated with each of these individual responsibilities?

My research study followed a hybrid Delphi research methodology comprised of the following elements:

i. Survey 1 - which explored the need for QRM role-based competencies.
ii. A Focus Group Workshop to identify standard QRM roles with the purpose of developing associated competencies.
iii. Survey 2 which presented the role-based QRM Technical and Behavioural Competencies identified and sought concurrence around the competencies for each role.
iv. Development of a Competency Model based on the findings.

Since October 2018 I re-focused the first research question on simply developing a QRM Competency Model Framework for individuals involved in the end-to-end product lifecycle. The first research question was modified as follows:

1. What are the roles and responsibilities of those involved in the end-to-end product lifecycle to achieve QRM effectiveness?

The second research question remained the same.

2. Background to the Research

The publication of the ICH Q9 Quality Risk Management (QRM) guideline (1) in 2005 has greatly impacted the biopharmaceutical sector. Fourteen years after Q9 the benefits of QRM are yet to be realised. The biopharmaceutical sector still struggles with implementation of Q9 principles in effectively assessing and managing product quality risks to ensure patient safety.

Waldron, in her thesis titled *Managing risk to the patient: Recoding Quality Risk Management for the pharmaceutical and biopharmaceutical industries*, (2) focused on organisational QRM maturity and did not evaluate how individuals can contribute to QRM effectiveness. She identified the need for role-based competency in QRM, and acknowledged that the traditional training model currently being employed in industry is inadequate in building such competency to enable a mature state in the management of risk to the patient. Waldron recognised that not all QRM practitioners require the same level of training and that competencies should be based on the level of involvement in QRM. This is also supported by Greene and Calnan, who identified that, while training is critical to QRM, it only teaches basic concepts to execute a task (3).

Byrne in her dissertation titled *An Investigation into Quality Risk Management Knowledge Held by Junior Quality and Manufacturing Roles in the Pharmaceutical Industry* (4) concluded that the pharmaceutical sector has not yet fully embraced QRM and has not yet fully understood the potential benefit of the analysis of risk to the patient. She highlighted the need to re-evaluate currently-used training methods and procedures for QRM users, and recommended incorporating QRM elements into GMP training and extending it to all GMP roles.

To develop role-based training for QRM users, the need for standardised GMP QRM roles emerged during the face-to-face focus group workshop mentioned earlier above. During the workshop it became apparent that QRM is not just the responsibility of dedicated QRM practitioners, but to be truly effective, is the responsibility of all those individuals involved in the end-to-end product lifecycle.

3. Individual QRM Roles

Based on the discussions and feedback from the face-to-face workshop, and in consultation with additional QRM practitioners, seven standard individual QRM practitioner roles were identified as presented in **Table 1** overleaf. Considering the hypothesis that all individuals involved in the end-to-end product lifecycle have responsibility for QRM, they are all regarded to be QRM practitioners.

In my opinion, characterizing the competencies needed to further advance QRM begins with defining the roles needed for a successful and effective QRM program. Then, based on the defined roles, competency mapping exercise is conducted to identify which key competencies are needed for those involved in QRM based on their role in the organization. **Figure 1** shows the QRM Competency Model that I have created to define the framework for advancing individual QRM maturity.

Individual QRM Roles	Definition
QRM Facilitator	Person(s) with the competence and skills to facilitate the QRM process as an independent QRM expert; Facilitate Quality Risk Assessment sessions and provide guidance for completion of QRM documents, risk control, risk communication, and risk review activities.
Quality Risk Assessment (QRA) Lead	Person(s) with the competence and skills to lead a risk assessment in terms of planning, completion, communication, review, and approval of QRM deliverables as well as tracking of risk controls measures; (in some companies this role is the same as a facilitator role, but in a company mature in the application of QRM principles, a QRA Lead is its own role)
Subject Matter Expert (SME):	Person(s) with the expertise in the area/topic being risk assessed who are able to provide technical expertise to support QRM activities including identification of hazards and implementation of risk controls
QRM Program Manager	Person(s) with the competence to develop and consistently deploy a QRM programme across manufacturing site/ operation within the area of responsibility
Other QRM Users	Person(s) with basic QRM understanding to apply it as an enabler to the Quality Systems. These include staff in all areas of GMP who are expected to apply risk-based principles within their work (e.g. change controls, deviations, batch record review, etc.)
Quality Unit Members	Person(s) with the competence to review, assess, and approve QRM documents within areas of responsibility, while ensuring compliance with internal Quality System requirements and external regulations.
Senior Management/Decision Makers	Person(s) with the competence and authority to make timely QRM decisions and who is authorized to accept the risk and direct response strategies for risk mitigation and follow-up. Person(s) with the authority to provide resources to conduct quality risk assessment and management activities, including implementation of risk control measures.

Table 1

4. Quality Risk Management Competency Model Framework

A competency model or competency framework is a description of the necessary competency to implement and complete successfully the work of a place, of a team, of a department or the whole organization (5). A competency framework can be described in many ways, one of which is described by the activities that are expressed during a job execution. Normally a competency framework is described in association with a title or a position of specific role, for example, the Society for Human Resource Management has developed a competency model in which a human resource professional should be competent in relation management, consultation, and communication, etc. (6).

A competency model should provide a definition for a competency, along with a means for measuring or observing that an individual can demonstrate a competency (7). Creating a competency framework is an effective method to assess, maintain, and monitor the knowledge, skills, and attributes of people in an organization (8). The framework shown in **Figure 1** is designed to allow the pharmaceutical sector to measure QRM competency levels to make sure QRM practitioners have the expertise needed to implement and sustain an effective QRM program. By identifying the specific behaviours and skills needed for each role, it enables the planning for training and development people really need.

In the QRM Competency Model I developed, each role has a structured description, a definition and more detailed description of the role. Then each role has a list of key competencies that provide supporting knowledge, skills and abilities needed for success, which are described as the set of technical and behavioural competencies required to perform a task or activity. The model includes indicators in the form of levels that define when a competency is achieved.

4.1 Delphi Survey II

The next phase of my Research is a Delphi 2 survey in support of the model in **Figure 1**. The purpose of this survey is to identify key areas of consensus and divergence among respondents on the need for QRM role-based technical and behavioural competencies.

4.1.1 Technical and Behavioural Competencies

A thorough review of competency-based models from academic and non-academic publications was conducted. Two main categories of competencies were identified as common among all models: Technical and Behavioural Competencies.

4.1.1.1 Technical Competencies

Technical competencies define what people have to know and be able to do (knowledge and skills) to carry

out their roles effectively. They are related to either generic roles (groups of similar roles), or to individual roles (role-specific co competencies). For example, a QRM Facilitator must have knowledge in the use of QRM Risk Assessment tools.

4.1.1.2 Behavioural Competencies

Behavioural competencies relate to types of behaviour which deliver effective results under such headings as team working, communication, leadership and decision making. They are sometimes known as soft skills. For example, if one needs to advocate risk management as a central part of an organisation's strategic management, then developing skills in Influence and Impact (a behavioural competency) would help achieve this.

4.2 Role-based QRM Competencies

Respondents were asked to rate the technical and behavioural competencies they believe apply to each role on a scale of 1-5 (1-Disagree, 2-Somewhat Disagree, 3- Uncertain, 4-Somewhat Agree, and 5-Agree)

4.2.1 Technical Competencies

The following technical competencies were presented to the respondents:

- 21 Competencies for Risk Assessment
- 7 Competencies for Risk Control
- 5 Competencies for Risk Communication
- 6 Competencies for Risk Review
- 16 Competencies for developing Quality Risk Management Strategy, Programme Design, Policy and Procedures.
- 13 Competencies for Risk Culture
- 7 Competencies for developing Risk Performance and Reporting

4.2.2 Behavioural Competencies

The following behavioural competencies were presented to the respondents:

- 16 Competencies associated with Facilitation Skills
- 14 Competencies for Leadership
- 11 Competencies for Decision Making
- 10 Competencies for Communication

The results of Survey 2, which will detail the role-based technical and behavioural competencies, will be shared in a separate publication.

Additionally, Lori Richter, a PRST PhD student, will be developing Quality Risk Management role-based training material based on the role-based competencies identified in this research. Lori has been researching Adult Learning Theory and application of various training modalities within general GMP training programmes within pharmaceutical and biotechnology companies. Now that the role-based competencies have been identified, Lori's research will now focus on expert interviews with adult education specialists to determine best practice approaches to teaching and coaching the competencies identified. The expert interviews coupled with the research performed within the adult learning space and GMP training programmes in the industry will lead to development of an effective QRM education and training programme.

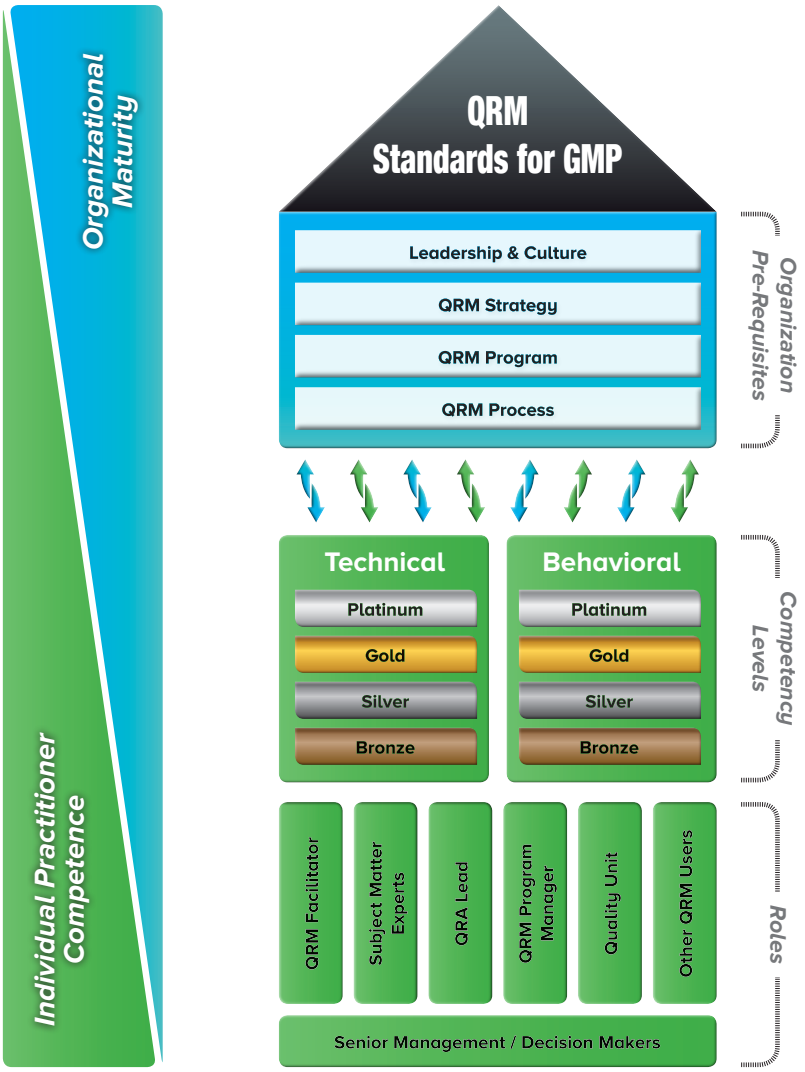

Figure 1: QRM Competency Model Framework

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5.3 QRM and KM in Innovation

Eamonn McGowran, QA & Regulatory Manager Klox Tech

The development of products in the life science sector, particularly in Pharmaceutical and Med Tech. fields, is multifaceted and complex, with inherent risk that a product in development will not succeed even after very substantial financial and time investment (1,2). Recent figures from the Tufts Center for the Study of Drug Development estimate that the cost for a pharmaceutical product from innovation to placing on the market - "bench to bedside" - comes in at around $2.7 billion (1,3) although some have expressed reservations about this figure and suggest it may be lower at $648 million (4).

In the biopharmaceutical and pharmaceutical sectors a number of pipeline problems have been identified. Whilst in the last ten to fifteen years increased expenditures on research have occurred in this sector, the number of new drug approvals has dipped (**1**). A recent study estimated that the overall success rates from Phase I to US FDA approval is roughly 9% (5). In a recent review, the European Medicines Agency (EMA) analysed Marketing Authorisation Approvals (MAAs) in Europe in the period 2010-2012. In this time span 94 MAAs for medicinal products containing a new active substance (NAS) received a positive opinion (6). Of these marketing authorisation holders, most (87%) were large or intermediate-sized pharmaceutical companies, and 13% were SMEs. In a further examination to identify who originated these compounds it is estimated that large or intermediate-sized pharmaceutical companies accounted for 49% of the products, SMEs for 27%, and academic/public bodies/PPPs accounted for 17%. Private–private collaborations accounted for 7%. The majority of the products originated by academic/public bodies/PPPs organisations were out-licensed to large or intermediate-sized companies (81%; 13 out of 16), with 19% (3 out of 16) being out-licensed to SMEs. Interestingly **none** of the academic/public bodies/PPPs which were the originators of their product retained the product to obtain a marketing authorisation.

Although academic institutions, public bodies and Public Private Partnership (PPPs) represent a very important source of innovation for the pharma and med-device sectors (6), their direct involvement in the development process tends to be limited to pre-clinical/very early stage development and they are not seen to be experts at bringing their product through the later stages of development and ultimately obtaining a marketing authorisation. Given the costs associated with the clinical development, and the increased regulatory complexities of the approval processes, it is not surprising that these bodies do not become involved in the later stages of product development and the approval process. What is clear is that by embracing regulatory knowledge the potential for increased involvement by the academic could be greatly enhanced (7). In developing a stronger understanding of regulatory science, academic institutions would be in a position to develop stronger ties with industry with further improvements in product development and realising successful licensing potentials (8).

Whilst regulatory processes are not intended to block or slow down drug development, many "academic developers" find navigating their complexities a difficulty (9). In addition, for academic institutes there appears to be a fear of communicating with regulatory authorities. On the other hand, many have a belief that they are the "experts" and, because of extensive peer review, believe less oversight is needed (10).

There is a disconnect in the principle in that :

- laws, regulations, and guidance shape the culture in a regulatory agency whereas
- success in research and peer review publication achievement is a culture within the academic community.

It is evident there is a large scope to improve the understanding of the academic community in the adherence and implementation of regulatory guidance that will allow for improvements and increased speed in innovation of products. Indeed, a paradigm shift may be required in how academics approach the development and ultimately commercialisation of their ideas.

Currently regulatory and commercial frameworks under which new medical products are supported throughout their development exists for SMEs in the EU, USA and other territories (11, 12, 13).

At the European level the European Commission has funded the STARS (Strengthening Training of Academia in Regulatory Science) programme with involvement of the regulatory authorities from 18 European countries (14). Its aim is to analyse and improve the training of academia in regulatory sciences on national and European level. This is linking in with the goals outlined in the recent European Medicine Agency 'Regulatory Science to 2025' strategy Goal 5: Enabling and leveraging research and innovation in regulatory science "***to develop the existing interaction between the EU regulatory network and academia further, in order to be kept informed of relevant scientific innovations and research and to identify solutions to regulatory needs and challenges***" (15)

Clearly with the above focus, new regulatory incentives for academics need to be developed to further facilitate engagement with regulatory authorities, not just for medicines but also other innovations in the life science healthcare setting (16, 17)

PhD research by the author at the Pharmaceutical Regulatory Science Team (PRST.ie) at Technological University Dublin in now under way in order to examine the steps to be taken to encourage and educate academic innovators in the need for early engagement with regulations and regulators. The major anticipated outputs of this research are to:

1. Elucidate the current understanding of regulatory science and incentives within the academic sector
2. Identify strategies to encourage the advancement of innovation from the bench to the market at academia by effective knowledge management/stewardship and appropriate risk management
3. Identify steps that can be taken by academic innovators in developing strategies to enhance further advances though invectives, education tools and enhanced regulatory interactions

4. Identify and recommend further incentives to foster and facilitate academic innovation
5. Outline opportunities to improve and accelerate product development through emerging new tools and technologies
6. Create a Regulatory Readiness Level (RRL) tool for academics that will allow for strategy design for product innovation and development with keys to appropriate regulatory science inputs. This tool will be used in the following ways:
    i. as a measurement system to assess the status of particular product in regards to its standing with regulatory requirements and suitability for approval
    ii. as an aid to academics to plan regulatory maps for innovations.

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Part 6: PANEL Questions and Answers Session

Panel members left to right: *Luke Kiernan, Paige Kane, Marty Lipa, Rick Friedman, Hal Baseman, John Lynch, Martine Nolan, Kevin O'Donnell*

Question/Topic 1

I would like to focus in the time we have left on the dynamics and tensions between the ***advancement of technology*** on the one hand, and ***regulatory science*** on the other hand, which are creating a regulatory *perfect storm* right now. Perhaps Regulatory Science Ireland can help solve some of this tension. Here's how I see it. We have the complexity of the processes and products that are dramatically increasing. We have accelerated review processes and shortened development times. We also have a relatively inflexible regulatory paradigm. It's aging, and it's relatively inflexible. So, there are tensions in this process. There is tension between the sophistication and potential of the science and the huge, vast potential of technology, Pharma 4.0 etc.

It is not essential to point out all of this, but there is tension in regulatory processes. What we need to do is to probe this a little. But the main tension has to do with change and the lack of flexibility around change, within countries themselves, and at a global level. So, if we start to probe the regulatory paradigm issue that advances in technology are racing ahead at this stage while regulatory science is less advanced.

Does anyone on the panel want to comment on this?

Responses from the Panel

Response 1:

We (in the FDA) have some Emergent Technology Teams (ETTs) and we have some PAT teams. CDER is very friendly to new technologies, with training in PAT, Isolators, closed systems. The fact is that we train in new technologies as we specialise more in the drug inspectorate. The Emergent Technology Team has a programme in place to give guidance, such as an e-mail address to send queries to, regarding new or innovative technologies. Even if we don't have ETT in place for the technology you are interested in, we still discuss things in our normal processes. FDA is ready for it, we have systems in place, we don't bite, we are human, we are happy to have a discussion with you, to give advice.

Response 2:

So, there are a couple of parts to my response. One is: I really think that what the previous panel member said does reflect reality. But, I think that to a large extent as an industry we have abdicated our responsibility for process control to the regulators. This is simply not fair. We are the experts in our processes and should know how to control them. When we either go to regulators and say what we would like to do, or accept recommendations from a regulator, It doesn't make good sense to abdicate that responsibility. To a certain extent: Shame on us! Regulations weren't set up to tell us how to control our processes. They were set up to judge if what we do is correct or not. I think that is a concept change that we need to do. So, as far as the regulators go, I think it would really help if there was a sharing of information as to what the criteria are by which the acceptability of technology is judged. What technologies out there have been accepted and what the reasons are. When I brought this up in the past the response was a lot of it is proprietary information, but that is just not true. Perhaps the information about the molecule you are using is proprietary, but for example, the use of different types of isolators is not really proprietary.

So, I was really intrigued by all the talk about knowledge transfer and knowledge management: that's all *intra*-company exchange of information. As an industry it would be pretty cool if we had *inter*-company exchanges of information. Individually we face challenges all the time in getting this to work, or that to work. But collectively we can probably solve any problem. So, as far as knowledge transfer and management are concerned, we would be pretty good if we could share more information.

Response 3:

Just to make another point. I do want to acknowledge that the regulatory affairs job is not an easy one. If you want to market in all the regions and all the countries concerned, the price you pay is to have to negotiate all those regulators.

The EU doesn't like it. The US doesn't like it. Japan doesn't like it, and we agree with industry and drove the ICH process to try to harmonise that, at least for these 3 regions. There are a lot of regions and countries left of course. But if you want a partner in Russia, Brazil, Turkey, etc, they well have a different system. I know that because I talk to a lot of people in industry all the time.

But you have chosen those markets, and if you choose to trade in these markets you are going to have to work it out with the regulators. For example, the US ended up agreeing with Japan that the supply chain system needed fixing and they harmonised it. In pursuing these regulators you have to apply the same philosophy. You have to say to them that the US and Japan realised they had to harmonise their supply chain system, and they did, you will have to work with the other regulators and apply the same pressure to bring it over the finish line.

Response 4:

There are parts of quality control that are inflexible. There are traditional approaches that are quite risk-averse. People can remember tribunals of enquiry and what politicians will ask if something goes wrong with a product. That does inform what we do. That said, there is scientific advice available for new processes at the European Medicines Agency. We can ask for advice there. We want to avoid the accusation of regulatory being too-close to the industry. There have been questions about that.

We (the HPRA) have an innovations office if anyone wants to talk to us about new technologies. It helps us to understand and it also helps us to advise around how this is likely to be regulated in the future. There are checks and balances there, but also there are ways to talk to the regulator, to know how your technologies will be considered in the future.

Moderator:

I think the message there is that there are channels for advice there, use them. Don't be afraid of them. One regulator has confirmed that 'they don't bite'

Question/Topic 2

A challenge for me, and I want to get the regulators' perspective on it!

I am a QRM person, so you can tell that I'm a big fan. I struggle with why the biopharmaceutical sector has more appetite for Lean Six Sigma than quality risk management. Why can we not use QRM to understand our processes, identify controls that we need to mitigate any risks in our processes? We don't believe that it adds value, or we can't actually convince our management, that it adds value. Yet we all use Lean Six Sigma champions and we have whole departments for it. But we don't get the same endorsement for Quality Risk Management. So, I invite responses from the panel about this.

Response 1:

I agree with what the questioner said. Industry will have to step up the game on risk management. Bring data and actually prove your point. We do ask the tough questions in the Agency.

On Lean Six Sigma, it's a good process. There are some excellent books on it, one from Professor Friedli, from St Gallen's University. There are great chapters in it. The good chapters point out that you can't lean out a process until it is stable, and what you lean out, really has to be risk. For example, if you have robust processes, can you eliminate inspections? It's not that you lean out inspections: it is that you don't have to rely on inspections. The inspection is valuable, but the point is you want to have to have as little waste as possible at the inspection.

Response 2:

Lean is about adding value. We don't really tend to measure the added value we get from QRM activities. We don't estimate using the risk ratings to get the risk reduction, and turn that into an argument about the increased quality assurance we have, and perhaps decreased use of valuable resources. This is hard to do when we don't have the tools to give us risk reduction measurements. We make risk reduction estimates all the time. With lean six sigma tools, and other approaches in lean, you do get more real-life measurements, which are occasionally cost measurements. Maybe this is one reason why you are not getting the benefit of the laborious work you do in QRM v's the other lean six sigma programmes mentioned. We are not there yet in terms of even remotely thinking about validating the risk assessment process, but we are making big decisions using risk assessment. This is one area we could consider working on.

Response 3:

A question to the audience as a follow up to the previous question.

If the collective regulators were to put an announcement out tomorrow that it is not necessary to use QRM at all, how many of your companies would stop using it?

Large show of hands

By answering in this way, do you mean a large number of companies would make decisions without considering the effect on patient safety and product quality. Probably not. That's the issue: we reflect the value of QRM to be something regulators want us to do, or to get in better standing with regulators – that devalues it. When we look at the success of six sigma and lean manufacturing which we are not doing because the regulators expect it, we are doing it for the shareholders.

Response 1:

The regulators considered QRM when they wrote the regulations. Every single GMP regulation is designed to mitigate a general risk in manufacturing.

'Thou shalt have procedures' to control your cleaning process, what is that doing? That is managing the risk that cleaning will be done in an uncontrolled way.

So, what is QRM all about?

It's simply understanding the specific risks, not the generic risks, embodied in the GMPs. That's all.

Response 2:

I used to do Six Sigma. The first step in Six Sigma is identifying the biggest risk you have in your processes and focusing on getting your SMEs just working on that. There is no point in trying to fix three things at once. *That right there is the problem I need to fix and I need to find the best way to fix it!* So, that is essentially Risk Management. It is risk identification the mitigation. Which further reinforces your point.

Question/Topic 3

My question is: are they not in parallel with each other? We really need to define understand our the processes. This is one of the core things with Lean and QRM. You are also developing metrics so that you can analysis how well you are doing them. Regardless of the driver, I think they both add a huge amount of value, and they complement each other very well, even if one is not a regulatory requirement.

Response 1:

I agree with you and I think they are very connected. We cannot do one without the other. But somehow it is Lean Six Sigma that comes before QRM. Leadership has more appetite for Six Sigma than for QRM. That is what I am struggling to understand. Why does the industry have more appetite for Lean Six Sigma than for QRM?

Moderator:

This in something close to my heart. Q10 is what motivated me to pursue doctoral studies focusing on protecting the patient and enhancing the outcomes by concentrating on the quality of the product. What I did was to bring the quality executives from three top pharmaceutical companies together with their Lean Six Sigma folks, to share the critical thinking with the Quality Executive. I like the term OpEx as it really is about building in excellence, which means you have a robust system, you have stable systems.

So, here's the headline: *What's good for the patient is good for the business.*

We regularly hear about OOT and OOS. OOS is there to protect the patient. OOT protects your business. If you are trending and monitoring, eventually you are going to use some of these industry 4.0 tools. If you really understand where your OOT is I guarantee you are protecting your business because the cost of poor quality is shocking. Nobody really counts it up. Nobody really looks at the annual accounts and says '*There's what it costs to fix everything we did not get right*'. Nobody counts it because it falls across so many different budgets. But it is something that we are trying to focus on at the moment, especially through PhD research on the cost of quality and on the business case for quality. The two actually go hand-in-hand because the business we in is delivering high quality products for the patient. So, we concede that there are tensions between systems. But there should not be. Manufacturers should pool all the resources of highly intelligent workforces to solve problems.

Question/Topic 5

This is a follow-on questions.

I do think Lean Six Sigma and QRM are a good match. But Lean Six Sigma did get hijacked by the OPEX people almost to the exclusion of a quality function. I think that in QRM there is a danger that the exciting profit controls we can see as the big-bang-for-your-buck and the problems that they might relieve, may have a role in undermining the function of the quality professional who is trying to develop PQS systems which are not always going to be based on process control, high investment control systems and big data. There is evidence of tacit functions in the operation as well.

So, my question is: What cautionary notes would you sound for the quality professional or quality director in an organisation to make sure that they can keep a hand on the rudder of PQS development?

Response 1:

I will answer this from a Knowledge Management perspective, not necessary for the whole PQS.

There has been a lot of recent talk around quality culture and when we look at knowledge management and QRM it's not so 'sexy' because it is a *Marathon and not a Sprint*. I would suggest, and be a little provocative here, that some of our senior managers thrive on results today, I fixed this problem today. There's not enough tolerance for making sure this problem does not happen. When I worked in quality operations I didn't want to do drama: that made my life harder. In essence we want to drama-proof our systems.

So what do we need to do then?

We need to understand our risks. We need to think thoughtfully about who are the people who have the knowledge? Are there ways we can convert the knowledge that is in people's heads and put it into the

business processes? We cannot get into the 'knowledge' heads' of these people. So, what happens when the Regulator show up for inspection? We identify the person with the knowledge and we pick up the phone.

Why do you have to do that?...

So, if our business processes were stronger and we really used the enablers , the tools of QRM and KM to manage the knowledge we have so that we have effective risk management. That does not mean merely filing in the data on a spread sheet. It means ensuring that you bring the best expertise to the table, having the right conversations. Then the knowledge should be reflected in the quality risk assessments.

Regarding QRM and KM, I think it was really insightful that it was put into Q10. But I don't quite understand how we use that to the best of our ability

That is just through my lens from a KM perspective.

Response 2:

I would just like to say something on two cautionary tales which I came across in the last 6 months or so. One cautionary tale is: it is going to get harder and harder to attract young talented individuals who are interested in technology. When I started my career, if you were interested in technologies you went to pharmaceuticals. Today, they don't want to go to pharmaceuticals. Nobody wants to get wet and dirty. They go to Silicon Valley. So, we have to be careful because if we talk about the great things that are out there we should keep this trend in mind.

The second cautionary tale is: I attended a talk some months ago where the discussions were about lack of improvements in the industry and about it being so stagnant.

We have regulatory issues. We have technological issues etc. Someone came up to me after the meeting and said, 'You know the way we are going to change things is to watch how companies like Amazon and Google are coming into our space. When they do this they are not going to put up with this stuff'.

Just some thoughts.

Question/Topic 6

Just in relation to quality culture, have any of the regulators seen the pharmaceutical companies embrace a quality culture? Have they seen any of the companies change their programmes? What might be used as a measurement of quality culture?

Response 1:

I don't do very many direct inspections now, but regarding measuring a quality culture, I suppose we could

look to senior management and how they focus attention on quality assurance, quality risk management and so on at the opening of inspection meetings. But we often during the inspection find that management commitment does not necessarily follow through. Sometimes quality processes are not quite in control, and there can be 'muddling through' with batches. This is not true for every case by any means. But, senior management does set the tone. If it is clear that senior management really won't tolerate sloppy practise in any organisation it is carried through in us finding very few issues. If there is a good quality culture at management level we see good product quality, fewer deviations, few complaints coming back. You can see a quality culture coming right through from the top of the organisation. In the European GMPs there is a huge emphasis on the role of senior management. Throughout the industry we believe that a quality management culture is really important. We put huge emphasis on the importance of the Qualified Person. That person is ultimately responsible for the release of a batch. If QPs are in a company where the quality culture is not quite right they will be under massive pressure. If they are not supported by senior management then, no matter how good they are, or how committed people are, there will be pieces of the quality jig-saw that don't fit properly.

Response 2:

A few things I would like to add to that with regard to Quality Culture, and in particular to key up the points of the previous speaker. Quality culture can be seen through things like: your cycle time, your on-time batch rate, your equipment capability and replacement of aging equipment, Capital investment in Manufacturing as an ongoing yearly expenditure, Supplier Management Programmes, Attentive Management of the supply chain, Taking ownership of supplier problems, Leadership visibility on the production floor showing their support, CpK measurements. These are leading indicators of Quality Culture, some are subjective, and not measurable, but some are tangible, such as checking your CpK or CAPA effectiveness.

Response 3:

With regard to quality culture, I would say that we have a very good 'compliance' culture. We sometimes do not distinguish between quality and compliance, especially if we meet all the tick-boxes. While we have a very good compliance culture we also need to ask why we are doing things to be compliant. We could ask if these things are the only things we could do. If there are other ways of doing things we should look at systems change. But we do tend to be very compliant in our behaviours.

Moderator:

Just following up that point. So, if we need to make the change from a 'compliance' to a 'quality' culture how do we do it? If we are looking at quality of final product we may need to go to 120 countries to ask them to make that change. Does that weigh in somehow?

Response 1:

Absolutely! This is one of the big challenges. It's a problem if we say we are not going to make changes to improve quality because it is too much of a regulatory burden. That is a problem. That's not right. How we fix it I don't know, but we need to do something.

While pharma in Ireland could be selling into 60, 70 or 80 different markets, the complexity gets bigger and bigger. We could get a change approved for one market in six months, but it could take up to three years to get approval in another. Basically then, we are running with slightly different products though all are compliant with local regulatory authorities. How do we manage our products between new and older versions? That is a real issue for us.

Response 2:

As long as we are still afraid of a high risk or red colour, or potential red colour, as long as we do not do things because we believe we have no money or resources to get things right first time. But we have a lot of money and multiple resources to do things over and over again. Then we do not have a good, mature quality culture. I think this is from benchmarking that still exists in some of our companies.

Moderator:

Could I add a note to that Please?

From being Chair of the ISPE cultural excellence team – we purposely called it 'cultural excellence' rather than 'quality culture' so that we might de-silo our businesses - not just to enable better knowledge management but because quality is actually everybody's business. So, once we can de-silo those businesses it is much easier to have an effective culture where there is no 'them' and 'us' with sets of checklists.

I would like here to comment on PDA where there is a fantastic assessment tool around quality culture. PDA and ISPE are working together for the first time on developing a 'root cause' guide.

So, there are tools out there. It does not really matter how many SOPs you have , how much training you have got, if culture is not healthy, you will not have a good product. So, think about investing in that team.

My last point is that achieving a quality culture is really difficult. But, after years of considering this, I came to the conclusion that it is all about behaviours. We should focus on behaviours and identify behaviours that contribute to good outcomes for your patient and your business. You focus on desired behaviours, and then reinforce these. You also identify behaviours that don't get the right outcomes first time and you eliminate them. If you start introducing change by means of behaviours it is much easier for people to digest that.

Part 7: Closing remarks by Professor Declan McCormack with acknowledgement of the panel of speakers, audience and organisers of the symposium.

It has been a real pleasure for me to attend this symposium today and to listen to the contributions of thought-leaders and doctoral research candidates. We realise many of you have travelled thousands of miles to be here to share your expertise with us so generously and honesty. I thank you sincerely. I wish to acknowledge our very effective Chair, Dr Pat O'Mahony, and our incredible audience of experts. Thank you for your attentiveness and continued interest in best practice in our sector and in big-picture thinking around all things regulatory science. I also acknowledge the important roles of our assistant students Laura and Katie, our photographers Claire and Michael, and audio recorder Roy Moore.

As you know we produced a monograph from the previous symposium late last year and we hope to produce a second monograph from today's event. In this regard I wish to thank Dr Anne Murphy for acting as curator for our events and for encouraging us to make proceedings available online and in printed format. We expect the second monograph based on today's proceedings to be available in June through the TU Dublin academic repository, jointly edited by TU Dublin colleagues with our HPRA colleague Dr Kevin O'Donnell. We will inform you all when that publication is available.

Great credit for initiating and organising this event goes to Professor Anne Greene, Dr Nuala Calnan and Dr Elaine Harris who foster the culture of knowledge-sharing and scholarship that is so evident today and which we value highly.

We hope you go away better informed, stimulated and with much food for thought.

Thank you again and safe home!

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